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Abstracts

Abstracts for the 44th Human Genetics Society of Australasia Annual Scientific Meeting, 14–17 August 2021

Oral Presentations

PLENARY 1
A Diagnosis for all Rare Genetic Diseases

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Accurate diagnosis is the cornerstone of medicine. Progress toward the discovery of the genetic basis of every rare disease (RD) has been substantial over the past decade, secondary to the introduction of exome sequencing. However, families with a RD often spend more than 5 years on a diagnostic odyssey of specialist visits and invasive testing that is lengthy, costly, and often futile. Despite our increased understanding of the mechanisms of RDs, the majority of patients remain undiagnosed because they do not have access to appropriate expertise and testing. For patients living in countries with more developed health-care systems, the current diagnostic paradigm for RDs is not designed for those who remain undiagnosed after initial investigations because of several challenges, including interpretation of test results and limitations inherent to the paradigm. An expansion of approaches in the clinic is required for undiagnosed RD patients including data sharing. Leveraging opportunities to participate in research programs that promote international sharing of deeper levels of data and utilize new technologies to understand RDs is an important path forward for patients seeking a diagnosis. Given recent advancements in such technologies and international initiatives, the prospect of identifying a molecular diagnosis for all patients with RDs has never been so attainable, but achieving this goal will require global cooperation at an unprecedented scale. This presentation will highlight approaches to RD discovery that will hopefully enable diagnoses for all such patients in the coming decade.

PLENARY 2
A Points-Based Approach to the ACMG/AMP Guidelines for Sequence Variant Interpretation

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Recently, ClinGen's Sequence Variant Interpretation (SVI) Working Group demonstrated that the qualitative American College of Medical Genetics and Genomics/Association for Medical Pathology (ACMG/AMP) guidelines for evaluation of Mendelian disease gene variants are fundamentally compatible with a quantitative Bayesian formulation. This quantitative Bayesian framework provides opportunities to further refine evidence categories and combining rules, and can support evaluation of appropriate strength-level criteria modifications to the guidelines. However, given that the actual use of Bayesian formulation can be challenging for some users because of the required calculations, the SVI WG further demonstrated a natural conversion from the Bayesian formulation into a points-based system. This points-based system results in thresholds of 6–9 points and ≥10 points for Likely pathogenic and Pathogenic, respectively, and thresholds of -1 to -6 and ≤-7 points for Likely benign and Benign, respectively. Additionally, the derived points per ACMG/AMP categorical strengths of Supporting, Moderate, Strong, and Very Strong are 1, 2, 4, and 8, respectively. The strengths of this system are its simplicity and that the connection between point values and odds of pathogenicity allows empirical calibration of the strength of evidence for individual data types. We conclude that a points-based system has the practical attribute of user-friendliness and can be useful so long as the underlying Bayesian principles are acknowledged.

PLENARY 3
What is Genetic About Cerebral Palsy?

Jozef Gecz[1,2] and The Australian Collaborative Cerebral Palsy Research Group

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Cerebral palsy (CP) is the most common physical disability of children, with approximately 500 children with CP born in Australia annually (1/700). CP is a heterogeneous group of nonprogressive disorders of movement and posture and is comorbid with intellectual disability (50%), epilepsy (33%), speech impairments (61%) or autism (9–30%). CP has been and continues to be understood as a 'brain injury-related' disorder and not routinely considered for genetic testing. Stem cell therapies, including autologous stem cell transplantation are frequent (26/46 registered CP clinical trials). Since 2014 we have pioneered systematic genomic investigations in CP as part of our Australian Collaborative Cerebral Palsy Research Group (n > 500) and International CP Genomics Consortium we established in Adelaide in 2017. Currently, we resolve about 30% of our CP Biobank cases using, WES, WGS, RNAseq, CP gene panels, or a combination of these. Internationally, about 3000 CP cases have been analyzed by WES or WGS with a mean ~30% (10.5–66% range) genetic diagnostic rate. More than 250 different genes have been involved in CP, largely

overlapping with known neurodevelopmental disability genes. Approximately 90 genes have been found a variant in CP cases more than once, e.g., *CTNNB1, KIF1A, COL4A1, STXBP1, or TUBA1A*. The current and prevailing understanding that CP is largely due to acute perinatal asphyxia (= brain injury) is being challenged. Given the known and emerging complexity of genetic etiology of CP together with its clinical heterogeneity, it is becoming clear that CP is not a unitary disease, but a partly genetic neurodevelopmental spectrum disorder.

PLENARY 4
Engineering CRISPR Models of Neurogenetic Disorders

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CRISPR genome editing technology enables targeted genetic modification of virtually any species with unprecedented efficiency. For biomedical research, CRISPR technology offers unparalleled opportunities to develop clinically relevant and sophisticated cell and animal disease models using virtually any species or cell type. Importantly, CRISPR can also be used to modify the human genome in vivo, enabling functional correction of disease-causing mutations for precision medicine applications. We have generated over 100 mutant mouse lines using CRIPSR. This presentation will describe our latest strategies to optimize genome editing in cells and mice, including the generation and analysis of mouse models of genetic epilepsy and intellectual disability that reveal new insights into the pathological mechanism and developmental origin of these debilitating conditions.

PLENARY 7
Impact of Personal Genomic Risk Information on Melanoma Prevention Behaviors and Psychological Outcomes: A Randomized-Controlled Trial

Anne E. Cust[1] and on behalf of the Managing Your Risk Study Group[2]

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Background: There is limited evidence for whether personalized genomic risk information motivates cancer prevention and early detection behaviors. *Aim:* We evaluated the impact of personal melanoma genomic risk information on sun-related behaviors and psychological outcomes. *Methods:* In this parallel group, open, randomized controlled trial, 1025 Australians of European ancestry without melanoma and aged 18–69 years were recruited via the Medicare database (3% consent). Participants were randomized to the intervention (n = 513; saliva sample for genetic testing, personalized melanoma risk booklet based on a 40-variant polygenic risk score, telephone-based genetic counseling, educational booklet), or control (n = 512; educational booklet). Wrist-worn ultraviolet radiation (UV) dosimeters (10-day wear) and questionnaires were administered at baseline, 1-month post-intervention, and 12-months post-baseline. Data were analyzed according to intention-to-treat. *Results:* At 12 months, 948 (92%) participants completed dosimetry and 973 (95%) the questionnaire. For the primary outcome, there was no effect of the genomic risk intervention on objectively measured UV exposure at 12-months, irrespective of traditional risk factors. For secondary outcomes at 12 months, the intervention reduced sunburns (risk ratio: 0.72, 95% confidence interval: 0.54 −0.96), and increased skin examinations among women. Melanoma-related worry was reduced. There was no overall impact on general psychological distress. *Conclusion:* Personalized genomic risk information did not influence sun exposure patterns but did improve some skin cancer prevention and early detection behaviors, suggesting it may be useful for precision prevention. Some effects differed by population subgroup. There was no evidence of psychological harm. Trial prospectively registered: ACTRN12617000691347.

PLENARY 10
Genomics and Therapeutics in Chronic Myeloid Leukemia

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Chronic myeloid leukemia (CML) is characterized by the BCR-ABL1 fusion, which causes activated and abnormal cell signaling. If untreated, CML progresses to a rapidly fatal acute leukemia at a median of 3 years. BCR-ABL1 can be superbly targeted by tyrosine kinase inhibitor drugs and most patients now have a life expectancy approaching that of the general population. However, about 20% of patients fail therapy and require a rapid change of treatment to avoid the risk of disease progression and death. Molecular monitoring of BCR-ABL1 transcript levels using quantitative PCR is now the recommended monitoring strategy and can predict treatment failure and detect emerging drug resistance. Acquired resistance is most frequently associated with mutations in the BCR-ABL1 kinase domain that interfere with drug binding. These are detected in ~50% of resistant patients, but the other resistance mechanisms are not well understood. Data is emerging from next-generation sequencing studies that somatic variants in cancer-related genes occur at a high frequency at drug resistance. Furthermore, these mutations have been detected in some patients at diagnosis and are associated with a poor outcome. Next-generation sequencing may provide important prognostic information for CML patients at diagnosis and resistance and identify targets for therapy.

PLENARY 12
Utility is Everything; Cancer Patients' Psychological and Behavioral Responses to Genomic Testing

P. Butow[1], M. Best[1,2], N Bartley[1], C. Napier[3], S. Vatter[1], D. Thomas[3], M. Ballinger[3], D. Goldstein[4] and and the PiGeOn Project team

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For genomic testing to fulfil its promise of enhancing cancer outcomes, patients and family members must be able to understand, process, and cope with genomic results. The Psychosocial issues in Genomic Oncology (PiGeOn) study is a substudy of the Molecular Screening and Therapeutics (MoST) program. MoST is recruiting adults with advanced or metastatic solid cancers, particularly rare and less common cancers, on their last line of treatment. Participants undergo comprehensive tumor genomic profiling (CTGP). Those with actionable findings are offered treatment in a related therapeutic trial if available. 1429 PiGeON participants completed questionnaires, and a subset semistructured interviews,

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exploring psychosocial issues and outcomes: prior to testing (T0), after receiving CTGP results (T1), and 2 months later (T2). Participants had only moderate knowledge of genomics, many desiring only the gist (having utility for their treatment). Many valued CTGP highly, seeing it as a last source of hope. Survival was their priority—other issues such as identification of a germline variant were seen as ancillary and even burdensome. The majority wanted all results, finding utility even in variants of unknown significance, which were seen as offering future hope should knowledge of their meaning emerge. Regardless of the results (actionable or nonactionable), results relieved future treatment uncertainty to some degree. Receiving actionable results, particularly if linked to immediate tailored treatment, improved psychological outcomes (anxiety and distress), but conversely, nonactionable results dashed hope. Self-efficacy and positive attitudes to uncertainty predicted improved psychological outcomes, and these may be a target for counseling and support interventions.

THE EVOLVING GENOMICS WORKFORCE PLENARY
Adaptable Workforce: Divergence Within Genetic Counseling

Barbara B. Biesecke

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Genomic medicine is incurring on routine health care. The most striking example is the CDC designation of testing for HBOC, Lynch syndrome, and familial hypercholesterolemia as Tier 1-appropriate for population screening. Without a US nationalized health care system, these tests are likely to be offered haphazardly. Studies to assess how interested people are, whether they make informed decisions and act on positive results will be critical to realizing benefits. Such advancements in clinical genomics policy suggest an urgency for general care practitioners to gain proficiencies in clinical genomics through medical and nursing schools and continuing education. Further, generating evidence of healthcare value will be key to the success of these advances. Within these care, expansions exist many roles for genetic counselors, yet there are insufficient numbers of certified counselors to meet growing needs. As such, genetic assistants will likely expand. These college graduates help to keep genetic counselors practicing at the top of their skill set. In addition, electronic resources will be increasingly used to augment, and even replace genetic counseling in routine circumstances. Evidence suggests that patients learn relevant information effectively from chatbots, freeing counselors to focus on counseling. This growing trend in diversifying genetic counseling practice and workforce should expand the reach to more people who may benefit from genomic testing. Yet, the relative tradeoffs are unknown. Genomic medicine predicts that aspects of genetic counseling will be provided by a wide range of professionals and resources; some shown to be effective and others as yet untested.

PLENARY 13
Advances in the Development of Targeted Therapies for NF1 Associated Peripheral Nerve Sheath Tumors

Brigitte Widemann

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Neurofibromatosis type 1 (NF1) is a common genetic tumor predisposition syndrome characterized by tumor and non-tumor manifestations. The development of peripheral nerve sheath tumors is a hallmark feature of NF1. Tumors include cutaneous neurofibromas, plexiform neurofibromas (PN), atypical neurofibromas and malignant peripheral nerve sheath tumors. Until recently there were no effective medical therapies for NF1 associated peripheral nerve sheath tumors. Through advances in the understanding of the pathogenesis of these tumors, the natural history of their growth and a series of clinical trials, several active medical therapies targeting PN have been identified. This includes MEK inhibitors. This talk will review key advances in the medical management of peripheral nerve sheath tumors and discuss ongoing research and future plans.

PLENARY 15
Clash of Hope and Hype: Is There a Case for a Stem Cell Counselor in Moderating Expectation in Stem Cell Science?

Megan Munsie

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For many in the community, the idea of stem cell science and regenerative medicine is synonymous with hope for a future free from suffering. Such hopes are fuelled by misrepresentation of 'miracle' cures in the mainstream media and online. Despite educational resources contextualizing progress made to date and the steps remaining to develop safe and effective stem cell-based products, it can be extremely challenging for patients and their loved ones to determine whether stem cell treatments are, or should be, an option for them. Aggressive direct-to-consumer marketing tactics by for-profit clinics looking to sell unproven interventions make this challenge even more difficult. This presentation will discuss the need for a more innovative strategy to strike a balance between maintaining community hopes while communicating the need for due process to responsibly deliver on the promise of this technology. While continued codevelopment of resources with consumer groups and healthcare professions is required, together with regulatory reforms to curb the exploitative and unethical commercial practices, it has also been suggested that patient decision-making could be greatly assisted by offering a professional service, such as a 'stem cell counselor'. Discussion will focus on the feasibility of extending the genetics counselor model to the field of regenerative medicine and other emerging technologies.

PLENARY 16
Precision Medicine in Ocular Disease

Alan Ma[1,2], John Grigg[1,3,4], Gladys Ho[2,5], Benjamin Nash[1,2,5], Bruce Bennetts[2,5] and Robyn Jamieso[1,2]

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Developmental eye disorders such as congenital cataracts and anterior segment dysgenesis are a major cause of childhood-onset blindness around the world. Similarly, inherited retinal disorders are a common cause of childhood and adult-onset visual impairment, and these disorders are all marked by significant clinical and genetic heterogeneity. Accurate genetic diagnosis is now increasingly vital for families to access gene therapies, and also accurate family recurrence risk counseling. In our large eye cohort genomic studies, we have uncovered a high rate of genetic diagnoses, and important lessons in the importance of careful gene curation, detailed ophthalmic phenotyping, and expert review of results and clinical features. Using a

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combination of panel and exome sequencing, we achieved a diagnostic rate of 70% in our patients with congenital cataracts. Subsequent whole genome analysis increased this to 77%. Exome and genome sequencing in the anterior segment patients found diagnoses in 54%. Many diagnoses were made in newly discovered genes, and also in novel phenotypic correlations. Studies in the retinal dystrophies have also revealed the value of genome sequencing in structural variant analyses and trio sequencing approaches. Key lessons from these studies have been translated into the diagnostic arena, and in the establishment of our ocular genomics multidisciplinary (MDT) review meeting. This is increasingly important as the availability of ocular gene therapies means having a genetic diagnosis is paramount. We have demonstrated the increased benefit of expert review to increase diagnostic yield, providing functional genomics avenues, and therapeutic options, to patients with genetic eye disorders.

PLENARY 17
Why Do Kids get Cataract? Fishing in the Genome for Answers

Kathryn P. Burdon

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Pediatric or congenital cataract is one of the most common causes of visual impairment in children. Cataracts in children can occur in isolation, but are also part of many syndromic or developmental disorders and are often one of the first features to be detected. Genetic testing for pediatric cataract can distinguish syndromic from isolated cataract and can minimize the diagnostic odyssey for children with developmental syndromes. At least 50 genes are recognized to cause isolated cataract and several hundred are implicated in syndromic forms, but genetic testing only reveals a pathogenic variant for 30–60% of children. Research continues to identify the remaining genetic causes and to understand the pathogenicity of variants in all cataract-related genes. Our laboratory maintains a large repository of DNA from children with inherited pediatric cataract and their families. Using genome sequencing and family-based linkage approaches, we are discovering new pathogenic variants, identifying novel genetic causes and exploring the role of modifier genes in disease severity for this predominantly monogenic disorder. We have established a moderate throughput CRISPR/Cas9 gene editing system in a zebrafish model to evaluate the role of novel genes in lens development and cataract formation. Our work is contributing to improved genetic testing for childhood cataract and expanding our knowledge of the molecular causes of childhood blindness.

PLENARY 18
Genetic Causes of Inherited Eye Disease in the Māori Population in New Zealand/Aotearoa

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New Zealand/Aotearoa is a small island nation at the bottom of the South Pacific, with a population of 5 million, and the largest Polynesian population in the world. 15% identify as Māori, and 7% as Pacific Peoples, and the spectrum of inherited eye disease encountered in this population varies from that seen in those identifying as NZ European. Keratoconus is more common, while primary open angle glaucoma is rare. A number of founder pathogenic variants have been elucidated in autosomal recessive ectopia lentis, and a common *PDE6B* variant causing up to 16% of autosomal recessive inherited retinal disease in the Māori population. Although many of those with inherited retinal disease remain genetically uncharacterized, research to date shows a range of novel variants in many genes. Understanding the population-specific genetic disease spectrum, clinical phenotypes, and a knowledge of regional ancestry and iwi (tribe), aids in simplifying the diagnostic process.

PLENARY 19
Specifications of the ACMG/AMP Variant Curation Guidelines for *MYOC*: Recommendations from the Clingen Glaucoma Expert Panel

Emmanuelle Souzeau[1], Kathryn Burdon[2], Jamie Craig[1], Patricia Graham[2,3], Johanna Hadler[1,4], Alex Hewitt[2], John Hulleman[5], David Mackey[2,3], Emi Nakahara[5], Francesca Pasutto[6], Owen Siggs[1], Terri Young[7] and Andrew Dubowsky[4]

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Background: Standardized variant curation criteria are essential for accurate interpretation of genetic results and clinical care of patients. The variant curation guidelines developed by ACMG/AMP in 2015 are widely used by the genetic community but are not gene-specific. The Clinical Genome Resource (ClinGen) Variant Curation Expert Panels (VCEP) are tasked with developing gene-specific variant curation guidelines. *Aim and Methods:* The Glaucoma VCEP was created in 2019 and assembled clinicians, researchers and laboratory scientists that aimed to develop and pilot rule specifications of the ACMG/AMP variant curation guidelines for *MYOC* variants, the most common cause of Mendelian glaucoma. *Results:* Among the 28 ACMG/AMP criteria, the Glaucoma VCEP adapted 15 rules to *MYOC* (including 10 strength specifications), while 13 rules were deemed not applicable. Key specifications included calculations of minor allele frequency thresholds, developing an approach to counting multiple independent probands and segregations, and reviewed functional assays that reported on the solubility and secretion of mutant proteins. The specified rules were piloted on 81 variants and led to a change in classification in 14/37 (38%) of those that were classified in ClinVar. Functional evidence led to the reclassification of 20 (45%) of VUS (including 13 from VUS to likely pathogenic and 7 from VUS to likely benign). *Conclusion:* The standardized variant curation guidelines for *MYOC* from the Glaucoma VCEP improved variant classification. *MYOC* variant curation and classifications will be submitted to ClinVar with expert-level status.

Mackenzies Mission: The Relationship Between ß-Ureidopropionase Deficiency Due to UPB1 Variants and Human Phenotypes is Uncertain

Sarah Righetti[1], Richard Allcock[2], Joy Lee[3], Louisa Adams[4], Carolyn Ellaway[4], Kristi Jones[4], Arthavan Selvanathan[4], Janice Fletcher[5], James Pitt[6], André B. P. van Kuilenburg[7], Martin Delatycki[6], Nigel Laing[8] and Edwin P. Kirk[5]

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Background: ß-ureidopropionase deficiency, caused by variants in UPB1, has been reported in association with varied

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neurodevelopmental phenotypes including intellectual disability, seizures, and autism. *Aim:* We aimed to reassess the relationship between variants in UPB1 and a clinical phenotype, in the light of available evidence including population databases. *Method:* Literature review, calculation of carrier frequencies from population databases, long-term follow-up of previously published case and report of additional cases. *Results:* Several of the variants previously reported as pathogenic are present at higher than expected frequencies for a rare condition. In particular, the most frequently reported variant, p.Arg326Gln, is very common among East Asians, with a carrier frequency of 1 in 20 and 1 in 907 being homozygous for the variant. Moreover, published reports include multiple individuals with mild or no phenotypes, as well as non-neurological presentations. *Conclusion:* Pending the availability of further evidence, UPB1 should be considered a 'gene of uncertain clinical significance'. Caution should be used in ascribing diagnostic significance to the identification of biochemical features of ß-ureidopropionase deficiency or UPB1 variants in patients with neurodevelopmental phenotypes. UPB1 is not currently suitable for inclusion in gene panels for reproductive genetic carrier screening.

SUBMITTED ORAL
Persistent Growth in Children with Achondroplasia Treated with Vosoritide for Two Years: Further Evidence Supporting the First Precision Therapy for This Condition

Ravi Savarirayan[1], Louise Tofts[2], Melita Irving[3], William Wilcox[4], Carlos A. Bacino[5], Julie Hoover-Fong[6], Rosendo Ullot Font[7], Paul Harmatz[8], Frank Rutsch[9], Michael B. Bober[10], Lynda E. Polgreen[11], Ignacio Ginebreda[12], Klaus Mohnike[13], Joel Charrow[14], Daniel Hoernschemeyer[15], Keiichi Ozono[16], Yasemin AlanayD[17], Paul Arundel[18], Shoji Kagami[19], Natsuo Yasui[19], Klane White MSc[20], Howard M. Saal[21], Antonio Leiva-Gea[22], Felipe Luna-González[22], Hiroshi Mochizuki[23], Donald Basel[24], Dania M. Porco[25], Kala Jayaram[25], Elena Fisheleva[26], Lynn Han[25] and Jonathan Day[26]

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Background/Objective: We report data from a pivotal, placebo-controlled, phase 3 trial and open-label extension study of 2 years of daily vosoritide treatment in children with achondroplasia aged 5–18 years. *Methods:* 121 participants enrolled in the phase 3 study; 60 received vosoritide and 61 placebo for 52 weeks. 119 entered the extension study; 58 continued treatment with vosoritide and 61 changed from placebo to vosoritide. Six-monthly AGV was analyzed from a baseline growth study, the placebo-controlled study, and 1 year of the extension study. An ANCOVA analysis was performed to assess the incremental gain in height in treated subjects as compared to subjects randomized to placebo after two years of follow-up. *Results:* Children randomized to receive daily vosoritide had a baseline mean AGV of 4.26 (0.20) cm/year, and children randomized to placebo 4.16 (0.16) cm/year. Mean (SD) AGV at 52 weeks was 5.39 (0.25) cm/year with vosoritide and 3.81 (0.17) cm/year for placebo. In the first year of treatment in the open-label extension study, the vosoritide treated children's AGV remained at 5.52 (0.27) cm/year. In participants who crossed from placebo to vosoritide, mean AGV increased to 5.43 (0.30) cm/year after 1 year of treatment. The comparative analysis showed that the LS mean difference (95% CI) in height gain after 2 years of treatment with vosoritide ($n = 52$) as compared to no treatment ($n = 38$), was 3.34 cm (2.76, 3.93). *Conclusions:* Vosoritide treatment results in safe and persistent growth in children aged 5–18 years with achondroplasia treated daily for 2 years.

ORAL 1
The Emerging Role of Whole Genome Investigation to Identify Undetected Nephropathies: The Hidden Study

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Background: 5% of patients commencing dialysis have an uncertain kidney disease etiology. New diagnostic approaches and tools are required. WGS is an emerging technology whose role in this setting is unclear. *Aim:* To determine the diagnostic yield of clinical whole genome sequencing (WGS) in individuals with unexplained end stage kidney disease (ESKD). *Methods:* Adult and pediatric patients reaching ESKD before 51 years of age without an identified etiology were prospectively recruited through a national network of 18 clinics. Eligibility was determined by a national clinical committee based on prespecified criteria. Clinically accredited WGS analysis was undertaken with a curated 'KidneyOme' virtual panel of genes associated with Mendelian kidney disorders (available in PanelApp-Australia). A genomic diagnosis constituted a KidneyOme result of pathogenic or likely pathogenic variant/s of appropriate zygosity. *Results:* 168 individuals were referred (2018-2021) of whom 147 were approved and 104 consented. Of these, 40 (38.5%) were female and median age was 43 years; 41 (39.4%) reached ESKD before 30 years and 63 (60.6%) had undergone native kidney biopsy. Of 50 results returned to date, 7 (14%) were diagnostic, including both autosomal dominant (4/7) and recessive (3/7) inheritance patterns with 6/7 having a family history of CKD. A further 14/50 had variants of uncertain significance. One diagnosis was due to a copy number variation. *Conclusion:* One in seven patients with ESKD of uncertain etiology had an undetected underlying monogenic cause for their kidney disease. Application of KidneyOme with WGS has diagnostic utility and should be considered in younger patients with unexplained renal failure.

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ORAL 2
An Easy Way to Convert Odds Ratios to Penetrance: Making Odds Ratios Useful in Clinical Practice

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Background: Odds ratios are commonly published in the literature to compare an affected cohort to an unaffected cohort. However, clinical interpretation of an odds ratio is challenging. *Aim:* We derive a formula for converting odds ratios to penetrance, the latter being more useful in a clinical setting, as it provides a percentage chance that the patient is affected. *Method:* We apply Bayes' theorem in a novel manner with relatively simple mathematics to create a formula that can be used by anyone with a basic calculator. *Results:* We show that an odds ratios of 22 for idiopathic pulmonary fibrosis are equivalent to a penetrance of <1%, while an odds ratio of 22 for intellectual disability is equivalent to a penetrance of 20%. More generally, we show how to convert any odds ratio for any condition into a penetrance estimate that is clinically useful for the patient. *Conclusion:* Odds ratios are difficult to interpret clinically but are widely used in publications. This formula is applicable across a range of fields and provides an easy way for the clinician to convert odds ratios into something more clinically meaningful for their patients. We provide a wide range of clinical utility for this relatively simple tool.

ORAL 3
Identification of Novel Molecular Pathways in Syndromic Orofacial Clefting

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Background: Syndromic orofacial clefting (OC) accounts for 30% of cleft lip and/or palate. An updated review of molecular pathways associated with syndromic OC is unavailable. *Aim*: To investigate molecular pathways associated with syndromic OC by reviewing the results of exome sequencing (ES) and exon-array CGH in a large cohort of patients with syndromic OC. *Methods*: Patients with syndromic OC were identified within the Deciphering Developmental Disorders study. Possible diagnostic variants were identified by automated variant filtering and manual review. SNVs within known disease-causing genes and CNVs were classified according to ACMG guidelines, ACGS Best Practice Guidelines and consensus opinion. Functional analyses of identified genes were performed within STRING, Cytoscape, and MCODE. Associated phenotypes were explored using the International Mouse Phenotyping Consortium. Gene expression analyses were performed within GENE2FUNC. *Results*: 603/13612 (4.4%) patients were identified of whom 453/603 (75.1%) had trio ES. Likely pathogenic or pathogenic variants were identified for 220/603 (36.5%) patients in 124 known disease-causing genes with *SATB2* the most common (16/220, 7.3%). 35 genes were identified that fulfilled criteria to be added to the PanelApp 'Clefting' panel. Gene ontology and pathway analyses identified novel molecular networks for syndromic OC which were distinct from those in nonsyndromic OC. Pathway and expression analyses showed an enrichment of genes associated with intellectual disability (FDR = 2.8×10^{-33}), RNA metabolism (FDR < 3.5×10^{-21}), transcription (FDR < 2.3x10-20), and chromatin organization (FDR = 1.03×10^{-11}). *Conclusion*: This study highlights novel molecular pathways specific to syndromic OC, enhances our understanding of lip and palate development, and increases the diagnostic rate for patients with syndromic OC.

ORAL 4
The *MECP2* Duplication Database (MDBase): Deep Phenotyping to Understand a Rare Developmental Epileptic Encephalopathy

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Background: MECP2 duplication syndrome (MDS) remains a poorly characterized, X-linked neurodevelopmental disorder caused by duplication of the methyl CPG-binding protein 2 (*MECP2*) gene, with an incidence of ~1/150,000 live births. Much better characterization of this disease is needed. *Aim:* A) ascertain a large population of patients with MDS to address the scarcity of phenotypic information and expand upon ill-defined features; B) compare acquisition of sitting, walking, and onset across other developmental epileptic encephalopathies (DEEs): Rett syndrome (RTT) and CDKL5 deficiency disorder (CDD). *Methods:* The international *MECP2* Duplication Database (MDBase) was established in 2020 to collect in-depth health-related data. Further data were extracted from the InterRett database (n = 619), AussieRett (n = 289), and International CDKL5 Disorder Database (n = 333). Descriptive statistics were used to report prevalence of comorbidities; time-to-event survival analysis was used to estimate median age of motor skill development onset. *Results:* Data were ascertained on 148 males (88%; med = 9.80 years) and 21 females (12%; med = 11.05 years) with MDS. Common comorbidities such as respiratory infections (119/143 [83%]) and epilepsy (90/146 [61%]) were highly prevalent. Previously poorly characterized features included fractures (46/138 [33%]), urinary retention (38/138 [28%]), and autonomic problems such as cold hands/feet (100/144 [69%]) and temperature regulation difficulties (82/145 [57%]). Developmental milestones delay in MDS was of intermediate severity compared with RTT and CDD. *Conclusion:* This is the largest case series on patients with MDS to date. Further natural history data is important for understanding how MDS develops with age, between males and females and for a better comparison with other DEEs.

ORAL 5
Insights from Five Years of Genomics Workforce and Education Research

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Aim/Methods: The Australian Genomics Workforce & Education program was tasked with: mapping the Australian landscape of

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genomics practice and education; assessing education needs across genomic workforce sectors; and developing tools to support effective genomics education and evaluation. Here we report results and deliverables from the five-year program. From 2016 to 2020, mixed-methods projects used desk-top audits, interviews, focus groups, surveys, and/or Delphi consensus process. *Results*:Data were collected from 1067 participants across 20 projects, including genetic and nongenetic clinicians (36 disciplines), education providers and evaluators (spanning 11 countries, 16 genomics alliances/consortia), relevant organizations, and system influencers. 54% of nongenetic specialists practice genomic medicine but only 25% feel prepared; 69.7% want support from Genetics services. The impact of different genomics topics and ways of learning suggests 'not all education is equal'. GPs access genomics education but genomics is yet to impact practice beyond NIPT. Other nonmedical health practitioners practice consumer-driven genomic medicine with limited access to impartial genomics education. Multidisciplinary workplace learning engenders increased confidence in acute care clinicians. In 2016 only 13% of Australian genomics education providers had education qualifications. We therefore developed tools: survey assessing genomic practice, attitudes and educational needs; program logic model to plan, develop, and deliver education; evaluation framework; and reporting standards to build an evidence base for effective genomics education. *Conclusion:* Our research provides evidence of adoption of genomic medicine, informing education as part of national implementation strategies. International collaborators are adapting our tools for local use. Factors facilitating workplace learning in genomics are now being explored.

ORAL 6
Population Genomic Screening of All Young Adults in Australia to Detect Familial Hypercholesterolemia: A Cost-Effectiveness Analysis

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Background: Familial hypercholesterolemia (FH) is a life-threatening inherited condition that causes high cholesterol and early coronary heart disease (CHD), affecting 1 in 250 Australians. FH is significantly underdiagnosed in Australia, with an estimated >90% of carriers remaining unidentified by current criteria-based genetic testing. *Aim:* To assess the impact and cost-effectiveness of offering population genomic screening to all young adults in Australia to detect heterozygous FH. *Methods:* We designed a decision analysis model to compare the current standard-of-care for heterozygous FH diagnosis (opportunistic cholesterol screening and genetic cascade testing) with population genomic screening of adults aged 18–40 years to detect pathogenic variants in the *LDLR/APOB/PCSK9* genes. The model captured morbidity/mortality due to CHD over a lifetime horizon, from a healthcare perspective. CHD risk, treatment effects, prevalence, and healthcare costs were estimated from published studies. Outcomes included quality adjusted life years (QALYs), costs, and incremental cost-effectiveness ratio (ICER), discounted 5% annually. Sensitivity analyses explored the impact of key input parameters on model robustness. *Results:* Over the population's lifetime (4,167,768 men; 4,129,961 women), the model estimated 62,722 years gained and 73,959 QALYs due to CHD prevention. Population genomic screening for FH would be cost-effective from a healthcare perspective if the cost per test was ≤AU$300, yielding an ICER <AU $28,000 per QALY gained. From a societal perspective, population genomic screening would be cost-saving. *Conclusion:* Based on our model, offering population genomic screening to all young adults to detect FH could be cost-effective in the Australian healthcare system, at testing costs that are currently feasible.

ORAL 7
Enabling Mitochondrial Donation in Australia — The Path to Legislative Change

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Background: Mitochondrial DNA (mtDNA) mutations cause severe health problems in ~60 individuals born in Australia each year. Mitochondrial donation (MD) can potentially allow couples to have a healthy child related to both parents who has healthy donor mtDNA. *Aim:* To describe the processes that led to legislation enabling MD to proceed to a conscience vote in Australia and how it is expected to roll out. *Methods:* The authors are mitochondrial researchers (DRT, JC) and CEO of the Mito Foundation (SM); all played lead roles in MD advocacy and will describe how the pending legislative change has been reached. *Results:* Following a series of scientific and ethical reviews plus community engagement, the UK legalized MD in 2015. In 2014, the Mito Foundation began lobbying for MD to be legalized in Australia, via encouraging families to speak with their political representatives plus direct lobbying of key position holders across the political spectrum. This led to a Senate Inquiry in 2018, followed by an NHMRC Expert Working Committee review and multiple forms of public engagement. In March 2021, the Federal Government introduced MD legislation that is expected to go to a conscience vote in mid-2021. In May 2021, the Federal Budget allocated $10M over 10 years to introduce MD into research settings in Australia and to facilitate a clinical trial. *Conclusion:* If MD proceeds in Australia, it will be a boon to affected families and the result of over 7 years of co-ordinated effort from families, scientists, clinicians, ethicists, politicians, and professional organizations.

ORAL 8
Reproductive Options for mtDNA Disease in Light of Current Australian Mitochondrial Donation Law Reform (Maeve's Law) Bill

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Background: Mitochondrial DNA (mtDNA) mutations can be maternally inherited or *de novo* and are often heteroplasmic.

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Given the clinical severity and lack of treatment, couples with an affected child may request preventing transmission to subsequent offspring. Due to limitations in phenotype prediction, prenatal diagnosis (PND) is only suitable if a high likelihood exists of offspring without mutation or mutation load below the expression threshold. This applies to mtDNA deletions and skewing mtDNA mutations. Preimplantation Genetic Testing (PGT) can be offered to heteroplasmic mtDNA mutation carriers with a higher (or unpredictable) recurrence risk, transferring embryos with mutant load below a mutation-specific or general expression threshold. For homoplasmic carriers, PGT is by definition not feasible and the same may apply to carriers with high mtDNA mutation loads. For those, mitochondrial donation, replacing the carrier's mitochondria with healthy donor mitochondria, can offer a solution. *Aim:* To assess, optimize and maximize reproductive options for mtDNA mutations. A summary of currently available techniques apart from egg donation will be presented from European experience. *Methods:* Systematic study of PND and PGT analyses for mtDNA mutations. *Results:* PND can also be offered to mothers of patients with most likely de novo mtDNA point mutations, which account for at least 25% of pediatric patients. In PGT, blastomere mutation load generally represents the whole embryo. *Conclusion:* Reproductive options are available for most mtDNA mutation carriers. Mitochondrial donation is currently in the process of (hopefully) being legislated in Australia and completes the portfolio of options to prevent mtDNA disease transmission.

ORAL 9
Genetic Landscape of Infantile Spasms With Focal Brain Malformations

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Background: Infantile spasms (IS) are a relatively common developmental and epileptic encephalopathy, typically arising between 4 and 8 months of age. IS are often associated with malformations of cortical development (MCDs). *Aim:* To investigate the genetic landscape of IS in individuals that underwent epilepsy surgery. *Methods:* We performed histopathologic review and genomic testing in 52 individuals with IS who underwent resective neurosurgery for seizure control at the Royal Children's Hospital, Melbourne. Genomic testing was performed on brain tissue using deep exome sequencing (n = 28), or targeted sequencing with a gene panel (n = 24). *Results:* Histopathologic analysis of brain tissue demonstrated tuberous sclerosis (TSC) (n = 22), focal cortical dysplasia (FCD) type I (16) and II (9) and nonspecific findings (5). The genetic basis of IS was identified in 35/52 (67%) individuals. Germline putative pathogenic variants were identified in 22 individuals, predominantly in genes associated with the mTOR pathway, such as *TSC2*, *DEPDC5,* and *PIK3CA*. Putative pathogenic somatic variants in brain (allele frequency ~1% to 41%) were identified in 13 individuals in *SLC35A2*, *AKT3*, *DEPDC5, and MTOR*. Brain somatic variants in *SLC35A2* were identified in most individuals with FCD I, whereas mTOR pathway variants were identified in most individuals with TSC and FCD II. *Conclusion:* The genetic landscape of IS with focal brain malformations comprises germline and brain somatic variants. Given the under-diagnosis of focal brain malformations, brain somatic variants are likely an under-recognized cause of IS. Our data highlights somatic variants in *SLC35A2* as a major cause of IS with focal malformations.

ORAL 10
Males with *FMR1* Premutation Alleles of Less Than 71 CGG Repeats Have Low Risk of Being Affected with Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

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Background: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset condition characterized by cerebellar ataxia and intention tremor, that can affect individuals with *FMR1* premutation (PM) CGG expansion (PM alleles — 55-199 repeats). Current penetrance estimates suggest 45% of males with a PM will develop FXTAS by age 80. *Aim:* To delineate FXTAS penetrance estimates for males based on PM CGG repeat size. *Methods:* Using pooled data detailing the incidence of PM alleles and corresponding CGG repeat size in nine adult onset ataxia cohorts (17/1,320 males), and PM rates in the community (61/41,847), we applied a Bayesian approach to calculate the probability of being identified with FXTAS as a function of allele size, assuming a lifetime risk of adult onset ataxia of 1 in 2000. *Results:* Our penetrance estimates suggest the risk of developing FXTAS for males with ≤70 repeats is less than 1% (0.031%; CI [0.007, 0.141]) which is over 40-fold lower than previously reported. Ataxia penetrance increases with allele size; 71–80 repeats (0.630%; CI [0.130, 2.992]), 81-90 repeats (3.074%; CI [0.806, 11.020]) and is greatest for alleles >90 repeats (4.542%; CI [1.749- 11.270]) with a broad confidence range reflecting a small sample size. *Conclusion:* In the absence of a family history of FXS, the risk of developing FXTAS for males with a PM of ≤70 CGG repeats is significantly lower than existing estimates. This data is critical to accurately counsel individuals with PM alleles, who are increasingly being identified through community carrier screening programs.

ORAL 11
The Role of AGG Interrupt Testing in Preconception Screening for Fragile X

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Background: Fragile X syndrome (FXS) is primarily due to the expansion of an unstable CGG repeat in the 5' UTR of *FMR1*. Premutation alleles (PM, 55-200 repeats) can expand to a full mutation (>200 repeats) upon a single maternal transmission; however, the risk is mitigated by the presence of AGG interrupts within the repeat

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region. *Aim:* To offer Australia-wide AGG interrupt testing with a turnaround time of <2 weeks to improve risk stratification for women with a low-range PM. *Methods:* The polymorphic (CGG)n triplet repeat was amplified by a modified Amplidex™ (Asuragen) PCR, in conjunction with an AGG-specific primer assay to provide unambiguous genotypes for PM alleles. *Results:* Since Jan 2020, 63 women were tested. The majority of these (57%) had a PM between 55-59 repeats, all of which carried at least 1 AGG interrupt and are not at risk of expansion to a FM. Overall 54 of the 63 women tested (86%) were considered to be very low-risk of having an expansion to a FM after AGG interrupt testing. *Conclusion:* AGG interrupt testing can better inform the risks for PM carriers, reducing unnecessary parental anxiety, counseling time and the need for invasive prenatal testing. We recommend that AGG interrupt testing be incorporated as a second tier test for low range premutations (55-69 repeats) in preconception screening, and only those <70 without AGG interrupts be reported as high risk. We are able to offer second tier testing for Fragile X screening for preconception programs.

ORAL 12
Clinical Impact of Whole Genome Sequencing in Early Onset Dementia Patients

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Background: Clinical genetic testing in early onset dementia (EOD) patients is challenging due to multiple types of diagnostic tests, undertaken through different laboratories, in order to arrive at a precise diagnosis. Whole genome sequencing (WGS) has the potential to serve as a single diagnostic platform for EOD genetics, due to its ability to detect common, rare, and structural genetic variations. *Methods:* WGS analysis was performed in 50 patients with EOD. Investigation of a targeted panel of 117 genes, followed by a 'Mendeliome' approach was undertaken. Subsequently, structural variant (SV) and short tandem repeat (STR) analysis were performed. An Alzheimer's disease (AD) age of onset specific polygenic hazard score (PHS) was calculated in patients with AD. *Results:* Clinically diagnostic pathogenic variants were identified in 7/50 (14%) of the patients. A further eight patients (16%) were found to have established risk factor alleles. All relevant variants were in the targeted set of genes with no additional findings through Mendeliome analysis. Two of the clinically diagnostic variants were identified through SV analysis. No expanded STRs were found in this study cohort, but a blinded analysis with a positive control identified a *C9orf72* expansion accurately. Nine of the 19 AD patients (~47%) had a PHS equivalent to >90th percentile risk. *Conclusion:* WGS acts as a single genetic test to identify different types of clinically relevant genetic variations in patients with EOD. WGS, if used as a first-line clinical diagnostic test, has the potential to increase the diagnostic yield and reduce time to diagnosis for EOD.

MULTIDISCIPLINARY ORAL 1
Lessons Learned From the First 170 Trios from the Genomic Autopsy Study

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Background: The cause of pregnancy loss and perinatal death remains unexplained in at least 25% of cases, despite a high perinatal autopsy rate in Australia. The Genomic autopsy study is a national collaborative study aimed at determining the cause. *Aim:* To apply WES/WGS to identify genetic causes of fetal/newborn abnormalities that result in termination of pregnancy, death in utero or in the newborn period, in view to providing families with answers regarding cause and likelihood of recurrence. *Methods:* WES/WGS is being performed on parent-fetus trios/quads following standard autopsy and noninformative microarray. High priority cases are consanguineous families, fetuses with multiple malformations, and unexplained fetal/newborn death. Statistical, bioinformatic, and experimental laboratory techniques are used to confirm causality of variants. *Results:* 170 prospective trios (150) or quads (20) have been recruited and sequenced. 89/170 (52%) are either solved or have a strong candidate gene identified. 42/170 (25%) of cases have been clearly solved by identification of a pathogenic mutation in a known gene. An additional 27/170 (16%) have a candidate variant in a known gene that expands phenotype. In 20/170 (12%) of cases, a mutation was identified in a gene not yet linked to human disease. *Discussion:* Our results provide justification for genomic investigation

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of pregnancy loss and perinatal death, particularly when congenital abnormalities are present. Establishing a clear diagnosis on clinical grounds alone is often challenging. Late stillbirth remains largely unexplained by genomics. Novel techniques for genomic investigation of unexplained stillbirth need further consideration, including genomic investigation of the placenta.

MULTIDISCIPLINARY ORAL 2
USP9X Associated Neurodevelopmental Disorders

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Variants in *USP9X*, an atypical X-chromosome gene that escapes X-inactivation, cause neurodevelopmental disorders (NDDs) in males and females, but by different mechanisms. Males are impacted by de-novo or maternally inherited hemizygous partial loss-of-function missense variants, while females are impacted by de-novo heterozygous complete loss-of-function variants. We now provide evidence of the contribution of *USP9X* missense variants in female NDDs also by reporting 14 likely pathogenic missense variants, arising de novo or inherited from mosaic mothers. Aggregate phenotypic assessment of 35 currently known females with pathogenic *USP9X* variation revealed a clinically recognisable *USP9X*-female syndrome. Comparison of this syndrome against all known male *USP9X* associated phenotypes highlighted shared neurological features, and discordant female-only congenital features. We thus used a brain-specific *USP9X* knockout mouse to investigate neuropathology. Consistent with human phenotypes, knockout mice displayed abnormal learning, memory, and communication. At a cellular level, advanced diffusion tensor MRI of knockout brains revealed deficits in major forebrain commissures, and identified long-range hypo-connectivity between cortical and subcortical regions. At a molecular level, *USP9X* encodes a deubiquitinating enzyme which promotes the stability and abundance of other target proteins. Using knockout mice, patient cells, and interrogation of all known USP9X target proteins, we show USP9X preferentially functions to stabilize proteins encoded by other NDD genes. Collectively, this new data expand, collate, and compare the genetic and phenotypic landscape of male and female *USP9X* associated NDDs, and reveal mechanisms of shared neuropathology involving disrupted neuronal connectivity and destabilization of proteins known to cause NDDs through loss of dosage.

MULTIDISCIPLINARY ORAL 3
Cancer Diagnosis Following Abnormal Noninvasive Prenatal Testing: A Case Series and Proposed Management Model

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Background: Noninvasive prenatal testing (NIPT) is a screening test for fetal chromosomal aneuploidy utilizing cell-free DNA (cfDNA) derived from maternal blood. It has been rapidly accepted into obstetric practice due to its application from 10-weeks' gestation, and its high sensitivity and specificity. NIPT results can be influenced by several factors including placental or maternal mosaicism and co-twin demise; cfDNA from a maternal origin can also complicate interpretation, with evidence that NIPT can detect asymptomatic maternal malignancies. *Aim:* This study aimed to develop management guidelines for women with NIPT results suspicious of maternal malignancy. *Methods:* The Peter MacCallum Cancer Centre's experience of seven cases where abnormal NIPT results led to investigation for maternal malignancy between 2016 and 2019 were reviewed, along with the published literature. *Results:* Six of the seven women (86%) were diagnosed with advanced malignancies, including colorectal cancer, breast cancer, melanoma, and Hodgkin's lymphoma. Reviewing the diagnostic yield of investigations preformed contributed to the development of the proposed guidelines, including the utilization low dose FDG PET-CT, which had a high concordance with other investigations and diagnoses. *Conclusion:* Based on our experiences, as well as a review of the literature, guidelines for the investigation and management of women with NIPT results suspicious of malignancy are proposed. These guidelines include maternal and fetal investigations as well as consideration of the complex medical, psychological, social, and ethical needs of these patients and their families.

MULTIDISCIPLINARY ORAL 4
Assessing the Contribution of Mosaic Genetic Variation to Cerebral Palsy Etiology

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Cerebral palsy (CP) results from nonprogressive damage to the developing brain and is the most common cause of childhood physical disability. At least 1/4 of individuals have an underlying genetic cause, with most variants arising de novo. This suggests that variants either: (1) arise during embryonic development (postzygotic mosaicism) or (2) are inherited from a germline mosaic parent. These mechanisms have different implications for recurrence risk and therefore, differentiating between them is important. We use genomic data from the Australian CP Biobank to assess the contribution of each mechanism to CP. We develop a pipeline using GATK, Mutect2, and MosaicHunter to identify somatic variants in parent-child trios, enabling identification of both germline and post-zygotic events. We also examine the causes of CP discordance in identical (monozygotic) twins, hypothesising that post-zygotic genetic variation could explain clinical discordance. We assessed both germline (i.e., shared between identical twins) and postzygotic (i.e., discordant in identical twins) genetic variation. For 5/13 twin pairs, we identified *de novo* shared variants of interest. In 1/13, we identified a novel *de novo* discordant missense variant in *MYT1L,* which we also validated by digital droplet PCR (alternate allele frequency:0.04 in CP-affected twin, 0.00 in unaffected twin). *MYT1L* drives neuronal differentiation by repressing the expression of non-neuronal genes and has been associated with intellectual disability. We are now performing functional analysis to assess pathogenicity

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of this variant. Together, these data demonstrate that genetic mosaicism is likely to be a rare but important cause of CP, with implications for estimating recurrence risk within families.

MULTIDISCIPLINARY ORAL 5
Specifications of the Acmg/Amp Variant Curation Guidelines for Myoc: Recommendations from the Clingen Glaucoma Expert Panel

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Background: Standardized variant curation criteria are essential for accurate interpretation of genetic results and clinical care of patients. The variant curation guidelines developed by ACMG/AMP in 2015 are widely used by the genetic community but are not gene-specific. The Clinical Genome Resource (ClinGen) Variant Curation Expert Panels (VCEP) are tasked with developing gene-specific variant curation guidelines. *Aim & Methods:* The Glaucoma VCEP was created in 2019 and assembled clinicians, researchers, and laboratory scientists that aimed to develop and pilot rule specifications of the ACMG/AMP variant curation guidelines for *MYOC* variants, the most common cause of Mendelian glaucoma. *Results:* Among the 28 ACMG/AMP criteria, the Glaucoma VCEP adapted 15 rules to *MYOC* (including 10 strength specifications), while 13 rules were deemed not applicable. Key specifications included calculations of minor allele frequency thresholds, developing an approach to counting multiple independent probands and segregations, and reviewed functional assays that reported on the solubility and secretion of mutant proteins. The specified rules were piloted on 81 variants and led to a change in classification in 14/37 (38%) of those that were classified in ClinVar. Functional evidence led to the reclassification of 20 (45%) of VUS (including 13 from VUS to likely pathogenic and 7 from VUS to likely benign). *Conclusion:* The standardized variant curation guidelines for *MYOC* from the Glaucoma VCEP improved variant classification. *MYOC* variant curation and classifications will be submitted to ClinVar with expert-level status.

MULTIDISCIPLINARY ORAL 6
An Approach to Genetic Counseling and Diagnostic Genetic Testing for Mnd and/or Ftd: Results of a Modified Delphi Consensus Survey

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Background: Genetic counseling and diagnostic genetic testing is part of the multidisciplinary care of people with motor neuron disease (MND) and/or frontotemporal dementia (FTD). There are no consistent, evidence-based genetic counseling approaches/guidelines for MND/FTD. Aim: Identify areas of consensus and conflict on the ideal components of genetic counseling for diagnostic genetic testing among various stakeholders, and propose a best practice statement. *Methods:* Experts in genetic counseling/testing for MND/FTD were invited, including health professionals (e.g. genetic health professionals, neurologists) and consumer experts (e.g., patients, relatives, MND/FTD support organization staff). An online, modified, multiround Delphi consensus survey was conducted using REDCap. Items in the first round were informed by two systematic literature reviews and qualitative interviews with consumers who had experienced diagnostic genetic testing. Descriptive and content analysis informed the development of the subsequent round and final results. *Results:* Forty-six experts participated: 100% completed round 1, 95.65% completed round 2. After round 1, items were updated based on comments regarding content and wording and presented for consensus in round 2. At survey completion, consensus was reached (>75% agreement) on all items, but there were conflicts regarding the timing of various discussions. Sixteen consensus items will be presented. *Conclusion:* The high level of consensus among health professionals and consumers indicates that the level of information, counseling, and support provided throughout the genetic counseling process should be adapted to the client's needs. The findings are critical as genetic testing becomes more routinely part of adult-onset neurodegenerative disease management due to emerging genotype-driven therapies.

MULTIDISCIPLINARY ORAL 7
Understanding the Needs of Adolescent and Young Adult Women Undergoing Predictive Genetic Counseling for Hereditary Breast and/or Ovarian Cancer

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Background: Adolescents and young adults (aged 15–25 years; AYAs) experience formative biopsychosocial development which has implications for the genetic counseling process. At the Parkville Familial Cancer Centre, Melbourne, AYA women are increasingly seeking predictive genetic testing for hereditary breast and/or ovarian cancer (HBOC), prior to the age of recommended risk management strategies (25 years). The specific genetic counseling needs of AYA women at this life stage have not yet been explored. *Aim:* This study explored the information and psychosocial support needs of AYA women who underwent predictive genetic testing for HBOC. *Method:* We conducted semistructured interviews with AYA women who underwent predictive genetic testing for HBOC and received results after January 2019. Reflexive thematic analysis was used to develop findings. *Results:* Nineteen AYAs (12 *BRCA1/2+ve*, 7 *BRCA1/2 or ATM -ve*) participated with a mean age at genetic testing of 21 years (range 17–24 years). Participants often found genetic counseling to be overwhelming, felt uncertain of their place in the health system and deprioritized their own needs to that of their loved ones, impacting their ability to process information and seek support. Test positive participants grappled with integrating the reproductive implications of their results into their view of the future, causing some participants discomfort and uncertainty. *Conclusion:* This study adds to growing evidence that AYAs require age-appropriate discussions and longitudinal specialized AYA care. Genetic health professionals should ascertain a young person's developmental stage, family dynamics and their future outlook to provide

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tailored developmentally appropriate genetic counseling that addresses their needs.

MULTIDISCIPLINARY ORAL 8
Evaluating Psychological Resources Codeveloped With Caregivers of Children With Genetic Epilepsy

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Background: Developmental and epileptic encephalopathies (DEE) are chronic and often life-threatening genetic conditions. Caring for a child with a genetic DEE is associated with a high risk of depression, anxiety, and chronic-traumatic stress. Caregivers report pervasive challenges accessing psychological support tailored to the realities and contexts of their child's diagnostic trajectory. However, acceptable methods of supporting caregiver psychological needs and adaptation to their child's diagnosis are unknown. *Aim:* We aimed to codesign and evaluate an empirically informed suite of audio-visual psychological resources tailored to DEE caregivers needs. *Methods*: We collaborated with caregivers using in-depth interviews (N = 25) and interactive focus group workshops (N = 8) to iteratively codesign the content of the psychological resources. Informed by this data, we co-produced six audio-visual resources, including caregiver quotes and practical psychoeducational summaries. We administered a web-based survey to assess the acceptability, relevance, and emotional impact of the resources, using validated and purpose-designed questionnaires. *Results*: Sixty-six caregivers, recruited from 10 international rare disease organizations and 4 tertiary children's hospitals reviewed and evaluated the resources. Caregivers rated the resources as highly acceptable and reported that they accurately represented their caregiving experiences and psychological support needs. Frequently described emotional responses included feeling 'comforted', 'hopeful', 'connected', and 'reassured'. Caregivers considered that providing the resources at diagnosis would address their need for reassurance and strengthen their coping skills. *Conclusion*: Our codesigned psychological resources appear to be acceptable and relevant to caregivers. Results suggest that these psychological resources offer valuable emotional support and can be delivered to DEE caregivers in healthcare settings.

MULTIDISCIPLINARY ORAL 9
Recording Our Genes: Stakeholder Views on Genetic Test Results in Networked Electronic Medical Records

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Background: Australia has seen rapid growth in clinical genetic testing and networked electronic medical records (EMRs): digital records that can be shared across different settings and may be patient-accessible. Incorporating genetic information into EMRs is a national policy priority to benefit care coordination and clinician decision making. Yet little is known about stakeholder views on its desirability and implementation. For instance, would patients prefer a more or less restrictive approach to genetic information accessibility? When should consent be sought for information access? What legal and information governance risks do clinicians perceive in networked EMRs? *Aim:* Within a project on legal and governance issues in the use of networked EMRs for genetic information, we aimed to examine the needs and concerns of patients, family members, patient advocates, and clinicians. *Methods:* We conducted semistructured qualitative interviews (mid 2021) and analyzed them using an inductive thematic approachin NVivo. *Results:* Preliminary data suggest: (1) Complex record-keeping systems have evolved to suit local clinical needs. (2) Stakeholders recognize the significance of the family context in the collection and disclosure of genetic information — both in determining individual risk and in familial health surveillance, prevention, diagnosis, and treatment. EMR design may evolve to better reflect this. (3) Laws, policies, and professional ethics protect individual health information but may fail to reflect family interests. Australian states and territories should pursue alignment with Commonwealth law on disclosing genetic information without patient consent (*Privacy Act 1988* (Cth) s 16B(4)). *Conclusion:* The interview findings will inform recommendations to address barriers to this national policy priority.

MULTIDISCIPLINARY ORAL 10
Metaphors and Why These are Important in Genetic Counseling

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Background: Metaphors appear simple but are fundamental schemata allowing expression and processing of complex emotions and information. Often so embedded in language and thinking that we are unaware of their impact, metaphor is recognized as a valuable tool in related fields of psychotherapy, education, linguistics, cancer care, palliative care, pain management, and counseling but has received little attention in genetic counseling aside from explanations for genes. *Hypothesis:* A deeper understanding of how to recognize and work with client-generated and counselor-generated metaphors has great potential as an addition to the genetic counseling 'tool-box'. *Methods:* This is a discussion paper, with reference to metaphor theory and studies from related health and psychotherapy fields, to present how working purposefully with metaphors may offer a powerful way to enhance communication within a reciprocally engaged client-counselor relationship. *Results:* Metaphors present ways to explain complex genetic concepts in a personally meaningful form, to gain a deeper understanding of client's experiences and emotions, to assist processing of experiences, emotions, and concepts, and to assist client and counselor to access and reflect on subconscious emotions, self-concept and motivations. In addition, working with metaphors has been shown to facilitate coping and action. *Conclusion:* This paper sets the scene for why and how genetic health professionals can utilize client-generated and counselor-generated metaphors purposefully to enhance the therapeutic interaction with clients.

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MULTIDISCIPLINARY ORAL 11
My Research Results: A Genetic Counselor-Led Program to Facilitate Return of Clinically Actionable Genetic Research Findings

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Background: Australian researchers increasingly support returning clinically actionable genetic research findings to participants, but may lack the skills and resources to do so. *Aim:* Develop a program to support researchers and facilitate the return of clinically actionable research findings to participants. *Methods:* The My Research Results (MyRR) program has been developed by a steering committee of clinicians, researchers, genetic educators, and consumers. MyRR supports researchers to return clinically actionable research findings to participants. MyRR is staffed by genetic counselors and available to researchers Australia-wide. Participants are notified of findings by letter, with a follow-up phone call from a genetic counselor. The MyRR experience of returning findings from the Melbourne Collaborative Cohort Study and the ASPREE Study is reported. *Results:* 23 individuals across the two studies were notified of clinically actionable findings from February to May 2021. Notification letters were sent to probands ($n = 21$) or, if deceased, the nominated next-of-kin ($n = 2$). MyRR genetic counselors successfully contacted 21 individuals (12 women, 9 men) regarding pathogenic variants in BRCA1 ($n = 6$), BRCA2 ($n = 13$), MSH6 ($n = 1$) and PMS2 ($n = 1$). The average age of notified probands was 81 years. Findings were disclosed to 20 individuals, one declined to receive the findings. Thirteen probands expressed an intention to attend a clinical genetics service for confirmatory testing and risk management advice. Five individuals were already aware of the findings. *Conclusion:* MyRR is a translational program promoting and facilitating access to clinically actionable genetic research findings, filling an important gap for Australian research studies and delivering health benefits to research participants.

MULTIDISCIPLINARY ORAL 12
Making Sense of Severity in the Context of Genetic Screenings

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Background: For interventions such as reproductive genetic carrier screening (RCS), severity is a key issue. This concept influences both the inclusion of a genetic condition on a screening panel and couples' subsequent decisions. Yet despite its crucial role, arriving at a specific definition of what severity means and how it can be applied to a range of genetic conditions remains elusive. *Aim:* We analyse severity as an ethically contested concept whose meaning is dependent on context and stakeholder role, and which can change over time. It is important for the design and implementation of programs like RCS to acknowledge and respond to this inherent complexity and uncertainty. Our conceptualization of severity achieves this. *Methods:* Our bioethical analysis of severity brings together both normative/theoretical and empirical investigations into this concept as it arises in healthcare decision making. We also critically evaluate attempts to develop objective approaches to quantifying severity in the context of genetic conditions. *Results:* Attending to different dimensions of severity helps anchor RCS policy and program design in a notion of severity that acknowledges the variability and uncertainty inherent in the concept, while still allowing it to play a crucial role in decision-making. *Conclusion:* While severity has an inherent uncertainty that depends on context and perspective, it is such a pivotal concept in RCS that we must find a way to explain and apply it clearly and consistently. Analysing its different dimensions is a way of bringing rigour to how severity is conceptualized.

MULTIDISCIPLINARY ORAL 13
Modelling Patient and Healthcare Services Outcomes From Applying Polygenic Risk Scores for Breast and Ovarian Cancer in Pathogenic Variant Carriers

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Background: Polygenic risk modifies breast and ovarian cancer risk in carriers of moderate and high-risk rare pathogenic variants (PV). The addition of a polygenic risk score (PRS) to genomic risk assessments would facilitate more personalized risk estimates and risk management advice, but the effectiveness of this approach is unknown. *Aim:* Estimate the long-term clinical and cost-effectiveness outcomes of a genomic risk assessment including a PRS for breast and ovarian cancer for carriers of PV in high/moderate-risk genes using microsimulation. *Methods:* A validated simulation model (miBRovaCAre) was adapted to include a PRS. The target population was cancer-unaffected women aged 20–39 years, with a PV (genes included *BRCA1, BRCA2, PALB2, ATM, BRIP1, CHEK2, RAD51C, RAD51D)*. Using accepted 10-year and lifetime risk management thresholds, the intervention was incorporation of a PRS to determine uptake and timing of risk management strategies, compared to current practice (based on the PV alone). *Results:* Introducing a PRS resulted in 0.16 quality-adjusted life-years saved per carrier at an average additional cost of $AUD1454, likely representing a cost-effective addition to current care. In general, the greatest benefit was seen in women in the highest quintile for PRS (breast and/or ovarian). An important contribution arose from improved personalization of the recommended age for risk-reducing salpingo-oophorectomy (RRSO). In women in the highest quintile of the PRS, the estimated average age of RRSO was reduced from 42.05 under current practice to 37.16 years by addition of the PRS. *Conclusion:* Tailoring cancer risk management through personalized germline risk assessments with a PRS could greatly benefit moderate- and high-risk PV carriers.

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MULTIDISCIPLINARY ORAL 14
Clinical and Laboratory Reporting Impact of ACMG and Modified ClinGen Variant Classification Frameworks in *MYH7*-Related Cardiomyopathy

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Background: ClinGen's expert panel adaptation of the ACMG guidelines provides gene-specific recommendations for interpretation of *MYH7* sequence variants in patients with inherited cardiomyopathy. *Aim:* We assessed laboratory and clinical impact of reclassification by ACMG and ClinGen in 43 *MYH7* variants reported by a diagnostic laboratory between 2013 and 2017. *Methods:* 52 proband reports containing *MYH7* variants were reinterpreted by original ACMG and ClinGen guidelines. Evidence items were compared across schemes and reasons for classification differences recorded. Laboratory impact was assessed by number of recommended report reissues, and reclassifications coded as clinically 'actionable' or 'equivalent'. Available pedigrees were reviewed to describe projected cascade impact. *Results:* ClinGen produced a higher proportion of diagnostic classifications (65% of variants) compared with ACMG (54%) and fewer variants of uncertain significance (30% versus 42%). ClinGen classification resulted in actionable changes in 18% of variants with equal upgrades and downgrades from original report. ClinGen's revisions to PM1 and PS4 contributed to classification differences in 21% and 19% of variants, respectively. Each classification change per proband report impacted, on average, 3.1 cascade reports with a further 6.3 first- and second-degree relatives potentially available for genotyping per family. *Conclusion:* ClinGen's gene-specific criteria provide expert-informed guidance for interpretation of *MYH7* sequence variants. Periodic re-evaluation improves diagnostic confidence and should be considered by clinical and laboratory teams.

MULTIDISCIPLINARY ORAL 15
Identification of an Oncogene Duplication By Genomewide NonInvasive Prenatal Screening

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Background: Genomewide noninvasive prenatal screening (NIPS) assesses for aneuploidy of all chromosomes, including segmental aneuploidy ≥7Mb. This can generate incidental findings that would not be identified by more focused NIPS platforms. Identification of multiple chromosome aneuploidies in cell-free DNA can suggest maternal malignancy. *Aim:* To provide an example of NIPS leading to the diagnosis of maternal malignancy and illustrate limitations of NIPS in the context of maternal malignancy. *Methods:* A 40-year-old woman presenting for routine prenatal screening had genomewide NIPS (Illumina VeriSeq NIPT Solution v2). The NIPS result was unhelpful for pregnancy assessment so combined first trimester screening was performed leading to chorionic villus sample testing. She had a standard clinical workup for malignancy of unknown origin. *Results:* NIPS revealed a fetal fraction of 13% with multiple genomic aberrations including monosomies on chromosomes 1, 2, 3, 4, 5, 10, 11, 17, and 18, and trisomies on chromosomes 6, 7, 9, 13, 16, 20, 21, and X. A duplication of the entire long arm of chromosome 8 was reported, including the *MYC* proto-oncogene region at 8q24.21, the first oncogene duplication found by NIPS. The patient was diagnosed with colorectal adenocarcinoma. SNP microarray analysis of the CVS sample revealed trisomy 21. Microarray performed on the tumor DNA found comparable results to the cfDNA; however, showed the tumor was disomic for chromosome 21. *Conclusion:* This case highlights the potential of genomewide NIPS to identify oncogene duplications and asymptomatic maternal malignancy as well as the potential masking of fetal aneuploidy by acquired maternal aneuploidies.

AACG ORAL 1
Integration of Genomic Testing in Mainstream Healthcare: Lessons from Oncology

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Background: 'Mainstreaming' is a proposed strategy to integrate genetic testing into oncology services, enhancing the identification of hereditary cancer and overcoming the barriers of genetics referral and clinician awareness. *Aims:* To identify health system interventions and implementation factors for mainstreaming genetic testing in oncology; to draft a mainstreaming oncology genomics model. *Methods:* Qualitative interviews and a quantitative survey with health professionals were conducted using the Consolidated Framework for Implementation Research. An exploratory cyclical design of two phases allowed the qualitative implementation data to inform the quantitative survey design. Theory-informed implementation data was collectively mapped to the Genomic Medicine Integrative Research framework. *Results:* The qualitative phase had 22 participants from 12 health organizations. The quantitative survey had 198 responses: 26% were genetic health professionals, 66% oncology health professionals, and 8% pathologists. The relative advantage and clinical utility of mainstreaming to improve genetic test access and to streamline care were identified. Optimization of current process was recognized for results delivery and follow-up. The barriers identified focused on funding, infrastructure and resources, and the need for process and role delineation for mainstreaming programs. Recommended interventions included improved communication and collaboration between specialties, embedded mainstream genetic counselors, electronic medical record genetic test ordering, with centralized results tracking systems, and development of dedicated resources. *Conclusions:* The Australian health system implementation factors identified informed the development of a preliminary mainstreaming oncology genomics model. Implementation and evaluation of this model are required to inform future mainstreaming initiatives and can translate to other disease contexts.

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AACG ORAL 2
Polygenic Score Modifies Risk for Alzheimer's Disease in *Apoe* E4 Homozygotes at Phenotypic Extremes

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Background: Phenotypic diversity in cognition among *APOE* e4 homozygotes can range from early-onset Alzheimer's disease (AD) to a lifetime with no symptoms of cognitive impairment. In this study, we investigated the role of polygenic risk between *APOE* e4/e4 phenotypic extremes as one of the explanations for this diversity. *Methods:* Using the clumping and thresholding method, based on a published genome-wide association study summary statistics, we evaluated a polygenic risk score (PRS) for AD, between cognitively healthy *APOE* e4 homozygotes aged ≥75 years (n = 213) and early-onset *APOE* □4 homozygote AD cases aged ≤65 years (n = 223) of European ancestry. Odds ratios (OR) for AD were calculated between the lowest 20% and highest 20% of PRS. *Results:* The PRS for AD was significantly higher in *APOE* e4 homozygote AD cases compared with older cognitively healthy *APOE* e4/e4 controls (*OR* 8.39; CI 2.0 to 35.2; p = .003). The difference in the same PRS between *APOE* e3/e3 extremes was not as significant (*OR* 3.13; CI 0.98 to 9.92; p = .053) despite similar numbers and power. There was no statistical difference in a PRS for educational attainment between the *APOE* e4/e4 or the *APOE* e3/e3 extremes, indicating that genetically determined education attainment did not act as a confounding factor. *Conclusion:* This *APOE* e4/e4 risk modifying PRS could contribute to improved risk stratification for those with the *APOE* e4/e4 genotype both in the research and clinical setting. It will also become more relevant as effective therapies for AD are developed.

AACG ORAL 3
Clinicians and Policy Reform: Towards the Best Outcomes for Patients With a Rare Genetic Disease

Nicole Millis

Rare Voices Australia

Background: Rare genetic diseases pose a significant collective burden in Australia. Diagnostic delays, together with limited access to treatments and health technologies, translate to a high level of unmet need in this patient group. The only way to see systemic changes for better care in this space is through effective policy reform. But how is this achieved? What is the role of clinicians in this work? *Aims:* A review of strengths and learnings from recent rare disease advocacy and policy activity, and the important role clinicians play in this. *Methods:* Case studies of recent national rare disease advocacy and policy activity in key policy areas, including the Life Saving Drugs Program, Newborn Bloodspot Screening, and the Parliamentary Inquiry into the approval processes for new drugs and novel medical technologies. Analysis of the role of clinicians and other stakeholders: Analysis of what is most and least effective in policy reform. *Results:* Clinicians lend real-world evidence and practical demonstrations of healthcare and clinical research to all stages of policy development. Their unique position enables a coordinated national approach to policy reform for integrated and innovative models of rare disease care. *Conclusion:* Effective policy reform cannot happen without strong advocacy and active collaboration. Clinicians and other stakeholders must work together at all stages in policy development to ensure nationwide systemic changes for rare genetic disease patients. Ongoing review of advocacy and policy reform activities would help ensure that this work remains strategic and effective in facilitating the best outcomes for patients.

AACG ORAL 4
A Model of Care for Clinical Implementation of Pharmacogenomics: Stage 1 of the Enact Study

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Background: Genetic factors contribute to inter-individual variabilities in response to pharmacological agents. Pharmacogenomics (PG) has been shown to significantly enhance clinical outcomes in mental illness treatment. Despite growing evidence, Australia has been slow in adopting PG testing to guide therapy. *Aims*: To understand the current knowledge and experience of PG testing in clinicians working in mental health. To propose a model of care based on the findings. *Methods:* A survey was created in RedCap to capture the knowledge and acceptability of PG testing, as well as the experience with PG, perceived barriers and resource needs for PG implementation, among clinicians working in the Psychiatry and Pharmacy departments in a single institution (St Vincent's Hospital Sydney). *Results:* While 42.9% of respondents agreed that PG testing would benefit their patients and 73.1% agreed that PG testing can identify medications which are likely to cause side effects, the majority of respondents (31/42, 73.8%) have never had discussions with their patients regarding pharmacogenomic testing. Thirty-three percent of respondents thought that PG testing was too expensive for their patient. Over half, 54.8%, of respondents do not feel confident discussing PG results with their patients and 47.7% of respondents felt that there needed to be more evidence to support PG testing before it is clinically relevant. *Conclusion:* We have identified barriers to PG

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uptake and usage (including cost, knowledge, and evidence) as well as potential strategies to overcome such barriers. We propose a model of care to PG implementation with a goal of integrating PG in future routine psychiatric care.

AACG ORAL 5
Recurrent De Novo Missense Variants in Gnb2 can Cause Syndromic Intellectual Disability

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Background: GTP-binding proteins (G-proteins) mediate signalling pathways involved in diverse cellular functions and comprise Gα and Gβγ units. Human diseases have been reported for all five Gβ proteins. A de novo missense variant in *GNB2* was recently reported in one individual with developmental delay/intellectual disability (DD/ID) and dysmorphism. We aimed to confirm *GNB2* as a neurodevelopmental disease gene, and elucidate the *GNB2*-associated neurodevelopmental phenotype in a patient cohort. *Methods:* We discovered a *GNB2* variant in an individual with syndromic intellectual disability via exome sequencing and sought individuals with *GNB2* variants via international data-sharing initiatives. In silico modelling of the variants was assessed, along with multiple lines of evidence in keeping with ACMG guidelines for interpretation of sequence variants. *Results:* We identified 12 unrelated individuals with five de novo missense variants in *GNB2*, four of which are recurrent: p.(Ala73Thr), p.(Gly77Arg), p.(Lys89Glu), and p.(Lys89Thr) (K89T). All individuals have DD/ID with variable dysmorphism and extra-neurologic features. The variants are located at the universally conserved shared interface with the Gα subunit, which modelling suggests weaken this interaction. *Conclusion:* Missense variants in *GNB2* cause a congenital neurodevelopmental disorder with variable syndromic features, broadening the spectrum of multisystem phenotypes associated with variants in genes encoding G-proteins.

AACG ORAL 6
Real World Outcomes of Clinical Exome Sequencing in an Adult Genetics Department

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Background; In addition to its technical advantages, falling testing costs and Victorian State Government subsidies have enabled whole exome sequencing (WES) to become a standard diagnostic test. There is extensive literature examining the yield and utility of WES in pediatric patients but no publications looking at WES in adult patients across all specialties written from a clinical perspective. *Aim;* To describe the clinical indications and quantify the diagnostic yield of WES in adults patients. A secondary aim was to examine the short-term clinical utility of WES in adults. *Methods;* Data including demographics, clinical indication, testing laboratory, cost, results, management changes, and cascade testing was collected for 250 consecutive patients who underwent WES through an adult genetics department between 2016 and 2021. Data were mainly analyzed using descriptive statistics. Testing where traditional gene panels were in standard usage, such as in heritable cancers, were excluded. *Results;* The average age at testing was 49 years (range 17–80). A diagnosis was identified in 27% patients and a likely diagnosis in a further 7.6%. Half of the patients with a diagnosis had immediate management changes. A third of patients with a diagnosis had at least one family member undergo cascade testing through our department. The results had reproductive implications for 16% of patients and 12% of family members. We also examined the clinical and age-related predictors of diagnostic outcomes. *Conclusion:* WES has a robust diagnostic rate and a clear clinical utility in adult patients across a range of phenotypes.

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AACG ORAL 7
The Role of Whole Exome Sequencing in Interstitial Lung Disease of Childhoood

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Background: Childhood interstitial lung disease (chILD) is a heterogeneous group of disorders often requiring life-long, complex care. Only a small proportion of cases have undergone genomic testing looking for a detectable monogenic cause. Most genomic testing has been based on a gene panel approach directed by the phenotypic presentation, with a reported diagnostic success rate of ~12%. No data currently exist using whole exome sequencing (WES) as the standard clinical pipeline. *Aim:* To assess the diagnostic utility of using WES in chILD with a hypothesis that WES would lead to an increased diagnostic rate. *Methods:* The chILD research, Australia and New Zealand (chILDRANZ) flagship, part of Australian Genomics, prospectively enrolled children between 2016 and 2020 from Australian hospitals, if the treating physician suspected chILD using agreed clinical criteria. Concurrently some critically ill infants were prospectively enrolled through the Acute Care flagship to access rapid testing. Trio WES was performed with an initial gene panel approach followed by trio exome analysis. *Results:* A total of 42 patients were recruited from multiple states and territories. Four patients were found to have clinically significant pathogenic variants, and two patients had variants of uncertain significance suspected to be the cause of their clinical phenotype. *Conclusion:* This was the first study to perform WES to look for monogenic causes of ILD in childhood. The diagnostic yield from WES in this study was 9.5% which was lower than expected and highlights the complex underlying etiology and likely combination of multiple common variants in conjunction with environmental factors.

AACG ORAL 8
Phenotype and Deep Sequencing in an Australian Tuberous Sclerosis Complex 'No Mutations Identified' Cohort

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Background: Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by pathogenic variants in the *TSC1* or *TSC2* gene with a prevalence of 8.8 per 100 000. TSC is associated with variable neurodevelopmental outcomes, seizures, and benign tumors in various organs. 10–15% of TSC patients have no pathogenic variants identified – the 'no mutations identified' (NMI) cohort. Previously, they have been reported to be phenotypically milder and likely have mosaic or intronic variants. *Aim:* To determine the phenotype of our NMI cohort, if testing multiple samples helps with diagnosis and to establish a testing strategy that may be viable in a diagnostic laboratory. *Methods:* We recruited 19 NMI patients from the TSC management clinic at Sydney Children's Hospital. We compared their phenotype with those with heterozygous variants. We designed a custom target capture panel consisting of the whole genomic region of *TSC1* and *TSC2*, and performed deep sequencing. A minimum of 2 samples was tested for each participant, including affected skin tissue (hypomelanotic macule, angiofibroma) where possible. *Results:* Our NMI cohort is not necessarily milder in phenotype. 17/19 (89%) of the patients had a likely causative variant found on deep sequencing, including 3 previously missed heterozygous variants, 10 likely germline pathogenic mosaic variants, and 5 suspicious mosaic variants. *Conclusion:* The majority of TSC NMI individuals are mosaic, but may not have a milder clinical phenotype. Testing multiple samples allows for the detection of germline mosaic variants on massively parallel sequencing without excessive cost and the need for specialized techniques.

AACG ORAL 9
Pathogenic Variants in Nucleoporin Tpr (Translocated Promoter Region, Nuclear Basket Protein) Cause a Neurological Phenotype in Humans

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Background: The nuclear pore complex (NPC) is a nuclear envelope multi-protein complex that regulates the trafficking of macromolecules between the nucleus and cytoplasm. Mutations in other components of the NPC have been shown to cause human disease, including neurological disorders, intellectual disability, and microcephaly. TPR is a critical scaffolding element of the nuclear basket, facing the interior of the NPC. *Aim:* Here, we present two siblings with biallelic variants in the *TPR* gene who presented with microcephaly, ataxia, and severe intellectual disability. We undertook functional validation to confirm pathogenicity of the novel variants. *Methods:* Whole genome sequencing and RNAseq were used to identify potential pathogenic variants, and to assess splicing of *TPR*. Patient fibroblasts were used to determine TPR protein levels

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and determine TPR-containing nuclear pore density, global nuclear pore density, and RNA distribution. *Results:* The variants result in a premature truncation codon causing nonsense-mediated decay, and a splice variant leading to a 12-amino acid truncation in a critical alpha-helical domain that provides structural rigidity to the nuclear basket. Functional analyses in patient fibroblasts demonstrate significantly reduced TPR protein levels, and decreased TPR-containing NPC density. A compensatory increase in total NPC levels was observed, supporting previous TPR knockdown studies. RNA levels were significantly reduced in the nucleus of patient fibroblasts. *Conclusion:* The discovery of mutations that partly disable TPR function provide valuable insights into the role of this essential protein in human disease, and our findings suggest that *TPR* variants are the cause of the patients' neurological disorder.

AACG ORAL 10
Novel Gene Discovery for Individuals with Rett Syndrome and Related Neurodevelopmental Disorders

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Background: Rett Syndrome (RTT) is a neurodevelopmental disorder (NDD) most often caused by mutations in the X-linked epigenetic regulator methyl-CpG-binding protein 2 (*MECP2*). However, RTT is genetically heterogenous, with approximately 2% of classic and 13% of atypical individuals without a genetic diagnosis. *Aim:* We analyzed sequencing data from *MECP2* mutation-negative patients, curated variants, and performed functional validation to reveal novel genetic bases for RTT and other associated NDDs. *Methods:* Whole genome (n = 2), exome (n = 3), and custom targeted sequencing (n = 1) was used to screen *MECP2*-negative RTT individuals for pathogenic variants, followed by *in silico* pathogenicity prediction, population frequency evaluation, evaluation of protein expression, and pre-established disease associations. Predicted pathogenic variants were functionally validated *in vitro* using cultured fibroblasts, Western blotting to determine extracted protein levels, and immunohistochemistry. *Results:* We identified potentially novel RTT-associated genes in these patients; of notable interest is an individual with a predicted pathogenic heterozygous *NUP188* missense [c.3922C>T, p.(Arg1308Cys)] on one allele, and a large (~287kb) chromosomal deletion spanning *NUP188* and *SET* on the other allele. *NUP188* encodes a scaffolding component of the nucleopore for macromolecule exchange, while *SET* is involved in transcriptional silencing, chromatin remodelling, and inhibition of histone acetylation, and has previously been associated with intellectual disability, speech and developmental delay. Our preliminary studies found decreased NUP188 expression and enlarged nuclei in cultured fibroblasts, consistent with NUP188 dysfunction. *Conclusion:* These newly identified genes expand current knowledge of the RTT genetic spectrum, flagging potentially pathogenic variants to assist in diagnosing elusive *MECP2*-negative RTT patients.

AACG ORAL 11
Speech and Language Deficits are Central to *SETBP1* Haploinsufficiency Disorder

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Background: Expressive communication impairment is associated with haploinsufficiency of *SETBP1*, as reported in small case series. Heterozygous pathogenic loss-of-function (LoF) variants in *SETBP1* have also been identified in independent cohorts ascertained for childhood apraxia of speech (CAS), warranting further investigation of the roles of this gene in speech development. *Aim:* To prospectively examine the speech, language, and literacy phenotype of a cohort of children with pathogenic LoF variants in *SETBP1,* using standardized tools. *Methods:* Thirty-one participants (12 males, aged 0; 8–23; 2 years) were assessed for speech, language, and literacy abilities. Broader development was also examined with standardized motor, social, and daily life skills assessments. *Results:* Gross and fine motor deficits (94%) and intellectual impairments (68%) were common. Childhood apraxia of speech (CAS) was the most common speech disorder (80%), followed by phonological disorder. Language was typically low, to moderately impaired, with commensurate expression and comprehension ability. Children were sociable with a strong desire to communicate. Minimally verbal children (32%) augmented speech with sign language, gestures, or digital devices. *Conclusion:* Here we expand the linguistic phenotype associated with *SETBP1* LoF syndrome (SETBP1 haploinsufficiency disorder), revealing a relatively homogeneous speech presentation implicating both motor (CAS, dysarthria) and language (phonological errors) systems. Overall, relative to general development, spoken language and literacy were poorer than social, daily living, motor and adaptive behavior skills. Findings show that poor communication is a central feature of *SETBP1* haploinsufficiency disorder, confirming this gene as a strong candidate for speech and language disorders.

AACG ORAL 12
Speech and Language Phenotyping in KAT6A Variants

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Background: Pathogenic KAT6A variants have recently been identified as a cause of syndromic neurodevelopmental disability. 'Speech delay' is commonly reported, yet no study has examined specific speech and language features in KAT6A syndrome. *Aim:* To expand

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the neurodevelopmental phenotype of KAT6A syndrome, with a focus on speech and language characteristics. *Methods:* Health, medical, and communication subdomains were assessed using descriptive and standardized measures, via online survey, and telehealth assessment. *Results:* 48 individuals with pathogenic KAT6A variants (1;8-31;10 years) were recruited. Truncating variants were most common (85%), with some missense and splicing variants. Individuals had intellectual disability (40% severe, 33% moderate, 19% mild) and 31% had autism. Other comorbidities included vision issues (76%), gastrointestinal problems (71%), sleep disturbance (66%), heart defects (46%), and microcephaly (52%). All displayed some form of communication impairment, with 75% relying primarily on nonverbal communication strategies. Verbal participants had a range of speech disorders, including speech apraxia (55%). Overall, most were severely impaired across adaptive functioning domains (daily living (91%), socialization (87%), communication (87%)) with late truncating variants consistently associated with greater difficulty. *Conclusion:* Severe communication difficulties are core in KAT6A syndrome, alongside a myriad of medical/neurodevelopmental comorbidities. Most are minimally verbal, and it can be difficult to delineate whether this relates to severe underlying motor deficits or severe linguistic impairment in the context of ID. Regardless, many rely on alternative means of communication beyond childhood (e.g. eye gaze, sign language). Alternative and augmentative options should be fostered as early as possible to allow for the best communication outcomes.

ASDG Oral 1
Somatic and Generational TTTTA/TTTCA Repeat Instability in Familial Adult Onset Myoclonic Epilepsy 2

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Familial Adult Myoclonic Epilepsy (FAME) is characterized by cortical tremor, myoclonus, and myoclonic and/or generalized tonic-clonic seizures. There are six autosomal dominant forms of FAME each caused by expansion of an intronic TTTTA repeat, as well as insertion and expansion of a TTTCA repeat in one of six genes with unrelated molecular functions. FAME2 maps to chromosome 2 and is caused by repeat expansion in intron one of *STARD7*. We previously showed anticipation for earlier FAME2 disease onset over three generations of a large Australian/NZ family; however, it was not determined if this phenomenon was correlated with the length of the repeat expansion. Here, we measured the length of FAME2 repeats in blood DNA from 94 affected individuals over 10 FAME2 families using long-range PCR, agarose gels, and Oxford nanopore long-read sequencing. Additionally, Bionano optical mapping was performed for four of these individuals. The estimated length of repeats were consistent between PCR-based and PCR-free methods. The average length of repeats increased in successive generations in multiple FAME2 families and correlated with age of onset of myoclonus ($r = -.329$, $p = .05$). Over successive passages of patient-derived lymphoblastoid and fibroblast cell lines, we further showed dynamic changes in repeat lengths; potentially modelling somatic instability. Finally, we detected FAME2 repeats using a novel technique to selectively nanopore sequence regions corresponding only to known genomic loci implicated in Mendelian repeat expansion disorders. This cutting edge approach has the potential for future application in amplification-free detection and sequencing of any known repeat expansion.

ASDG ORAL 2
Collaborative International Data Aggregation and Analysis for Rare Hematological Cancer Predisposition Syndromes Caused By Germline *RUNX1*, *DDX41* and *GATA2* Mutations

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Background: Hematological cancer predisposition syndromes (HCPS), caused by germline variants in known genes including *RUNX1, DDX41, and GATA2,* have been studied for decades; however, challenges remain to improve patient outcomes[1]. Disease heterogeneity, small patient-cohorts, lack of identification/appropriate classification of variants, remains a significant challenge to our understanding of these syndromes. To help overcome these challenges, an international effort is required to collate and standardize disease-specific clinical and genomics data, accumulating enough data to make evidence-based clinical decisions. *Method/Results:* Collating phenotypic and genetic information extracted from peer-reviewed literature, and international colleagues, we created a standardized clinical resource for germline *RUNX1 (gRUNX1)* HCPS (RUNX1database:https://runx1db.runx1-fpd.org/snpdb/index). We created a registry of *gRUNX1* variants expertly curated and classified according to ACMG/AMP gene-specific criteria, including 258 *gRUNX1* probands/families and 164 unique *gRUNX1* variants. Utilizing the collective wealth of NGS data

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generated from international laboratories, we created the largest *gRUNX1* genomics cohort: 179 *gRUNX1* NGS datasets, including both pre-leukemic(65) and malignancy(62) samples. Interrogating this dataset as a single cohort, we have identified novel somatic mutational patterns in pre-leukemic samples before progression to AML, including recurrent mutations in several clonal hematopoiesis genes including *BCOR*. We are currently expanding this initiative to both *gGATA2* and *gDDX41* HCPS. *Conclusion:* Aggregation of families, individuals, and disease stages into a centralized database where all data undergo rigorous quality control will aid in the exploration and discovery of the molecular progression of these syndromes. Providing a resource to inform evidence-based clinical decisions on molecular monitoring and a framework for the development of therapeutic interventions to prevent leukemia development.

ASDG ORAL 3
Splice-Switching Oligonucleotide-Mediated Correction of a Deep Intronic Splice-Variant in *Timmdc1* in Cells of Patients with Severe Early Onset Neurodegenerative Disorder

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Background: Combined analysis of genome sequencing (GS) and RNAseq data from patient-derived cells or disease-relevant tissues have been particularly effective in identifying disease variants with splicing or gene-regulatory effects. Splicing variants represent up to 13% of the known pathogenic variants and offer great opportunity for the development of treatments. *Aim:* To use Splice-Switching Oligonucleotides (SSOs) to correct perturbed mitochondrial function due to a deep-intronic, homozygous *TIMMDC1* c.596+2146A>G, cryptic splice-site activating variant (allele frequency 1/10,000), in patients with severe early-onset, progressive, neurodegenerative disorder. *Methods:* We used GS and RNAseq (fibroblasts) analyses of two children and their consanguineous parents to identify the *TIMMDC1* variant. We confirmed aberrant TIMMDC1 mRNA splicing and undetectable TIMMDC1 protein in two patient fibroblasts. We designed two different SSOs to target the *TIMMDC1* deep intronic variant in patients' cells. *Results: TIMMDC1* encodes the Translocase of Inner Mitochondrial Membrane Domain-Containing protein 1 subunit of complex I of the electron transport chain responsible for ATP production. *TIMMDC1* variant causes infantile-onset neurodegenerative disorder manifesting with a predominant sensorimotor axonal neuropathy, optic atrophy, and cognitive deficit. We showed that *TIMMDC1* enhances aberrant splicing, leading to an insertion of a poison exon that introduces a premature stop codon (p.Gly199_Thr200ins5*) in the TIMMDC1 mRNA rendering it susceptible to NMD. This leads to undetectable TIMMDC1 protein and compromized mitochondrial complex I function in the patient fibroblasts. Using SSOs, we completely restored normal *TIMMDC1* mRNA, protein, and mitochondrial function. *Conclusion:* We provide proof of principle correction of the molecular defect underlying this severe neurological disorder.

ASDG ORAL 4
MBS Testing For Exomes: Review of the First 12 Months

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Background: SA Pathology has provided NATA-accredited exome testing since 2015 but uptake was limited due to cost of testing. In 2020, exome testing was added to the Medical Benefits Scheme (MBS). *Aim:* We review the outcomes of the first 12 months of MBS-funded exome testing. *Methods:* An audit of the number of referrals, diagnostic outcomes, and implementation challenges were performed. *Results:* Despite clinical and laboratory disruptions due to COVID-19, over 230 cases were referred (77% trios, 23% singletons). Trio requests were reported more rapidly and had fewer VUS (16% vs 30%) compared to singletons. Overall diagnostic rate was slightly higher in trios (32%) than singletons (27%). As expected, the majority of trio diagnoses were due to de novo variants (67%), with an additional 9% X-linked, 7% compound heterozygous, and 4% homozygous variants detected. Surprisingly, 11% of diagnoses involved inherited dominant disorders that were either mosaic or had variable expressivity in a parent. Detection of carrier status for unrelated conditions and VUS presented reporting challenges. Workforce training and managing the additional workload is proving to be a significant and ongoing challenge. Urgent requests have also increased in frequency. One such example was a pregnant couple with a 16-month-old child in which we established a diagnosis of Filippi syndrome and could confirm in a clinically relevant timeframe that the fetus also carried the variants. *Conclusion:* Our experience has highlighted a number of challenges for laboratories offering MBS-funded exome testing but has also corroborated the clinical utility of the testing.

ASDG ORAL 5
GeneMatching Candidates From the Genomic Autopsy Study to Elevate Variant Classification for Prenatal Clinical Use

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Background: Trio analysis from the Genomic Autopsy Study revealed that a molecular diagnosis can be ascertained in half of clinically unresolved cases of early miscarriage or perinatal death (n = 89/

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170). However, only half (n = 41/89) of these putative disease genes can be used prenatally for assessing recurrence risk, despite compelling evidence from available animal models, gene constraints, and expression data. The ACMG guidelines are heavily weighted towards existing genotype to phenotype delineations in the post-natal setting, which can confound the interpretation of prenatal cases, with little to no hindsight on severe or lethal in utero presentations. *Aim:* Assess the proportion of cases with variants and/or genes of uncertain significance, which can be reclassified based on identifying additional kindreds from genematching. *Methods:* Between 2018 and 2021, we submitted 35 genes to the genotype matching platform, MatchMaker Exchange, to seek additional, unrelated kindreds with similar clinical phenotype and/or initiate collaborations with expert curators of genes or disease subgroups for each case[2]. *Results:* We received matches for 33/34 gene submitted, with an average 7 participants responding per gene and contact initiated between 1 and 25 months after submission. The genematching identified additional kindreds with clinical overlap (10/33) and/or initiated functional validation (5/33) and diagnosis for publications (3/33). *Conclusion:* Phenotype matching is critical for clinical interpretation, which can be accelerated through the use of genotype sharing platforms like MatchMaker exchange. Additional kindreds can be identified in a fifth of cases with variants or genes of uncertain significance.

ASDG ORAL 6
Routine RNA follow-up of Genomic Analysis to Prove Causality of Variants of Unknown Significance

Peer Arts[1], Thuong T. Ha[1,2], Andrew Dubowsky[3], Parvathy Venugopal[1], Leila Eshraghi[1], Alicia B. Byrne[1,4], Oliver van Wageningen[3], Duncan Holds[3], Jinghua Feng[1,2], Paul Wang[1,2], David Lawrence[1,2], Nick Warnock[2], Tian Zhiyu[2], Song Gao[3], John Toubia[2], Roula Ghaoui[5], Sunita de Sousa[1,6,7], Milena Babic[1], Sarah L. King Smith[1], Matilda R. Jackson[1,8], Andreas W. Schreiber[2,9], Karin S. Kassahn[3] and Hamish S. Scott[1,2,4,7,8]

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Background: Mutations altering mRNA splicing (splice variants) contribute up to 9% of pathogenic variants underlying genetic diseases, which is likely an underrepresentation and biased towards canonical splice sites. Identifying splice variants among variants of unknown significance (VUS), outside of canonical splice sites is aided by bioinformatic predictions. However, clinical interpretation of these splice variants remains challenging without follow-up RNA experiments. *Aim:* Optimize RNA follow-up experiments, across various research and diagnostic projects, to validate and determine the pathogenicity of predicted splice variants. *Methods:* Patients from all ages with candidate variants predicted to cause aberrant splicing (multiple bioinformatics algorithms) were selected for our validation study. Based on tissue and RNA availability, and gene expression, we performed polyA RNAseq, RNAseq capture, or (M13 primer tagged) gene-specific RT-PCR coupled with Sanger (clinical testing) or long-read (Pacbio and Nanopore) sequencing. *Results:* Collectively, clinical evaluation of 99 different splice variants by RT-PCR and Sanger showed altered splicing for 53/99 variants, of which 38/53 were at canonical splice sites (+/-10bp). More recently, mRNA sequencing and long-read sequencing of RT-PCR products revealed altered splicing for 10 variants, upgrading their classification to (likely) pathogenic. *Conclusions:* RNA analysis provided evidence of aberrant splicing in 62/109 patients, guiding variant interpretation. For poorly expressed genes in available (proxy-) tissues, sequencing of RT-PCR products remains advantageous over RNAseq. In addition, the single molecular nature of recent (short and long-read) sequencing technologies allowed phasing of the variant or a heterozygous SNP to the observed splice effect.

ASDG ORAL 7
From Vous to Gene Therapy: A Stem Cell Based Approach to Determining the Pathogenicity of Novel Ocular Genomic Variants

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Background: Genomic studies of our Australian retinal dystrophy cohort in a clinical diagnostic setting are providing clear-cut molecular diagnoses in ~50% of families examined; however, assessing pathogenicity of novel genomic variants can be challenging. This is especially relevant where there are strict inclusion criteria for emerging gene therapies. Patient-derived induced pluripotent stem cells (iPSCs) differentiated to retinal pigmented epithelial (RPE) cells or retinal organoids provide a valuable resource for investigation of genes with retinal-specific expression. *Aim:* The aim of this study was to determine the pathogenicity of a novel synonymous *RPE65* variant of unknown significance detected in trans with an established pathogenic variant on diagnostic genomic testing, in siblings with early onset severe retinal degeneration. *Method:* iPSC cells were generated from the peripheral blood of a heterozygous *RPE65* synonymous variant carrier. Gene expression studies using qRT-PCR and immunohistochemistry were performed to confirm pluripotency and subsequent differentiation to RPE. RNA was extracted from iPSC-RPE cells, with Sanger sequencing performed to investigate splicing aberrations. *Results:* Gene expression studies of iPSC and subsequent RPE lines confirmed pluripotency and presence of RPE-specific markers, respectively. SNP chromosome microarray studies of iPSCs confirmed genomic stability. Analysis of RNA from carrier parent iPSC-RPE demonstrated exon skipping in the *RPE65* transcript, and a predicted mutant *RPE65* allele of only 22 amino acids. Reduction in *RPE65* expression was observed. *Conclusion:* These findings facilitated the variant's reclassification to pathogenic, and further showcase the importance of synergistic stem cell studies and diagnostic genomics in the era of gene therapies.

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ASDG ORAL 8
Does Advanced Paternal Age Increase the Rate of Paternally Derived AneuploidaAs Detected by SNP Array?

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Background: Studies investigating the impact of paternal age on the incidence of embryo aneuploidy using young oocyte donors have reported conflicting results. This study takes a different approach, which is to look at the parental source of embryo aneuploidy as detected by SNP array. *Aim:* To determine whether the incidence and type of paternal-origin aneuploidy increases with advancing paternal age. *Methods:* A retrospective study of 1541 embryos with SNP array testing from 2012 to 2020 across three paternal age groups: <35 years (n = 410), 35–40 years (n = 789) and >40 years (n = 315). The primary outcome was frequency of paternally derived aneuploidy in each age bracket. The secondary endpoint was the comparison of rates of specific and complex aneuploidies of paternal origin. *Results:* There was no significant association between advancing paternal age and prevalence of paternal-origin aneuploidy (<35 years: 17.8%, 35–40 years:16.2%;>40 years:17.1%). Moreover, no significant differences were found between age cohorts in the occurrence of paternal-origin trisomy and paternal-origin monosomy. The rate of paternally derived complex abnormalities increased with advancing paternal age (<35 yrs: 2.9%, 35–40 years: 3.8%; >40 years: 4.4%) but did not reach statistical significance. Analysis of specific chromosomes showed the >40 yrs cohort to have a marked increase in rates of trisomy 4, 10, 12, and 19. Unlike previously reported, no clear difference was observed in the rate of trisomy 21 with advancing paternal age. *Conclusion:* We conclude that there is no association between paternal age and the overall rate of paternal-origin aneuploidy. However, our findings suggest a possible effect of advanced paternal age on the rate of paternally derived complex abnormalities, as well as increased rate of specific paternal-origin trisomies.

ASDG ORAL 9
Integrated Analysis of Exome Case-Control and Tumor Sequencing Data from High-Grade Serous Ovarian Cancer Patients Reveals Potential Novel Predisposition Genes

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Background: High-grade serous ovarian carcinoma (HGSOC) has a significant hereditary component, half of which is currently unexplained. We recently reported enrichment for germline loss-of-function (LoF) variants in 43 candidate genes among 510 *BRCA1/2*-negative HGSOC patients. However, as the number of carriers for each gene was small, orthogonal approaches are needed to validate these findings, leading us to conduct tumor sequencing to seek molecular genetic evidence of biallelic inactivation of these genes in germline carriers. *Methods:* Whole exome, Sanger, and targeted bisulphite DNA sequencing were performed using archival HGSOC specimens from 89 patients who were heterozygous germline LoF variant carriers for candidate genes or previously proposed genes (e.g. *PALB2*). Data were analyzed for copy number loss, somatic point mutations, promoter methylation and mutational signatures. *Results:* Of the proposed genes, *PALB2* and *ATM* displayed biallelic inactivation in nearly every tumor from germline carriers. For candidate genes, 19 of 38 studied demonstrated biallelic inactivation in at least one tumor from a germline carrier. One gene-*LLGL2*- emerged as a promising candidate, displaying biallelic inactivation in every sequenced sample and a distinctive mutational signature with low homologous recombination repair deficiency, similar to others' and our own sequenced *ATM* tumors with biallelic inactivation. *Conclusions:* Our results for *PALB2* demonstrate the utility of this approach for validating candidate familial cancer genes, providing further support that this is an HGSOC predisposition gene. Using this methodology, several candidate genes demonstrated evidence of tumor wildtype allelic inactivation to indicate a potential predisposing role, worthy of further investigation.

ASDG ORAL 10
Clinical Utility of Next Generation Sequencing in the Diagnosis and Management of Myeloid Malignancies

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Background: Next Generation Sequencing (NGS) has an increasingly recognized role in the diagnostic workup, management, and monitoring of patients with myeloid malignancies. At our institution, a NATA accredited myeloid NGS targeted panel is offered to all patients with clonal myeloid disorders including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPNs). To highlight its value, we sought to describe the real-world use and clinical utility of NGS panels. *Methods:* Patients' samples were analyzed by a 31-gene custom-designed panel using Anchored Multiplexed PCR technology with molecular barcodes. Curation was done with standardized bioinformatics utilising error correction for highly sensitive and accurate variant calling. *Results:* 1102 samples were processed over a 3-year period. Mutations were found in 88% of AML (n = 189/216 cases), 86% of MDS (n = 74/86 cases), and 98% of MDS/MPN overlap patients (n = 39/40 cases) with morphologically confirmed diagnosis. 95% of MPN patients had mutations (n = 117/123 cases), majority of which were driver mutations (*JAK2*, *CALR*, *MPL*). Amongst cases of suspected MDS with indeterminate morphological features, 30% of cases had clonal mutations. Amongst cases of suspected MPN due to persistent abnormal blood counts, 13% had clonal mutations. Our data also uncovered novel and low allelic frequency variants that were missed by conventional assays and thus helped in supporting the diagnosis in few cases. *Conclusion:* NGS testing has a powerful impact in myeloid malignancies for conforming diagnosis, shape prognosis, and guide management choices including targeted therapies. However, challenges remain in routine availability, funding, and expertise needed for curation and variant interpretation.

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ASDG ORAL 11
Evidence Sharing Across Australian Clinical Genetic Testing Laboratories Via Shariant Platform Aids Variant Interpretation

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Background: Sharing genomic variant clinical interpretations across laboratories is recognized to improve diagnostic accuracy and patient management[1]. Australian Genomics initiated an implementation project to improve variant interpretation in the Australian setting. *Methods:* In consultation with Australian public and private clinical genetic testing laboratories, Shariant was designed as a controlled access platform to allow inter-laboratory automated sharing of structured evidence for clinically curated variants. Shariant was also developed to support a process to automatically identify and promote resolution of variant interpretation discrepancies. *Results:* To date, ten clinical genetic testing laboratories across four states have contributed >7000 prospective variant interpretations to Shariant. Connection of another nine laboratories from three states is in progress. Approximately 10% (15) of variants with classifications from multiple laboratories have been identified as discrepant across the tiers (Likely) Pathogenic, Variant of Uncertain Significance, (Likely) Benign; 73% (11) are medically significant differences. Seven discrepancies have already been resolved, attributing changes to review of structured evidence (2), segregation evidence from one laboratory (1), new published functional evidence (1), review of an out-of-date classification (1) and a low penetrance/risk allele (1). Assessment of ACMG-AMP[2] code usage and weight for (Likely) Pathogenic and Uncertain Significance variants identified inter-laboratory variability for application of PS4 (prevalence in affected individuals over controls, ~25% of records), and PS3 (functional analysis, ~16% of records). *Conclusion:* These findings demonstrate the feasibility of implementing a national variant sharing platform, highlight advantages of using structured evidence to resolve inter-laboratory discrepancies, and present possible areas for variant curation standardization across Australia.

ASDG ORAL 12
Systematic Follow-Up to Redefine Recurrence Risk of De Novo Mutations Leading to Perinatal Death

Peer Arts[1], Thuong T. Ha[1,2], Alicia B. Byrne[1,3], Matilda R. Jackson[1,7], Milena Babic[1], Tristan S.E. Hardy[4,5], David Lawrence[2], Sarah L. King-Smith[1], Alan McGovern[1], Thessa Kroes[6], Mark Corbett[6]Genomic Autopsy Study Research Network, Jozef Gecz[6], Karin S. Kassahn[4,9], Andreas W. Schreiber[2,9], Christopher P. Barnett[8,10,#] and Hamish S. Scott[1,2,7,9,#]

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Background: The Genomic Autopsy Study investigates the genetic underpinnings of perinatal death; the loss of a fetus or neonate. To date, exome and genome sequencing in 170 families has yielded 47 (27.6%) causative variants and 41 (24.1%) candidate variants, of which 42 (48%) were called de novo. Follow-up of these de novo mutations is not routinely performed in genetic pathology laboratories; with recurrence risks counselled at 1%. *Aim:* To systematically assess parental mosaicism for de novo variants involved in perinatal death, to allow more accurate counseling on actual recurrence risk. *Methods:* We performed phasing for 42 de novo variants using existing genomic sequencing data (N = 17) or Nanopore sequencing (N = 25) to identify the parental origin. In addition, we applied custom droplet digital PCR (ddPCR) assays to determine presence of the specific variant in parental blood (31), saliva (11), and sperm (4). *Results:* Similar to earlier reports, 80% of autosomal de novo mutations were phased to the paternal allele. Follow-up by ddPCR revealed paternal mosaicism for 4/29 (14%) variants tested to date, with variant allele frequencies ranging between 0.05% and 10% in blood samples; the latter corresponding to 20% in sperm. While the variant was not called by the GATK haplotypecaller, the (10%) mosaicism could be visualized using IGV. *Conclusion:* Autosomal de novo mutations underlying perinatal death occur on the paternal allele in 80% of cases. Using somatic variant callers, manual inspection in IGV and assessment of low-level mosaicism by ddPCR facilitates more accurate counseling regarding recurrence risks for future pregnancies.

ASGC ORAL 1
What is the Impact of *Brca1/2* Status on Young Women's Reproduction and Relationships after Predictive Testing? An Australian Case-Control Study

Laura Forrest[1,2], Rowan Forbes Shepherd[1], Louise Keogh[3], Mary-Anne Young[4], Lucinda Salmon[5], Linda Warwick[6], Jo Burke[7,8], Rachel Williams[9,10,11], Catherine Beard[1], Rebecca D'Souza[12] and Paul James[1,2]

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Background: Predictive testing for the high-risk cancer predisposition genes *BRCA1/2* in young women has unique implications for relationships and reproductive choices. Although explored thematically in the past, the impact of these issues has not been quantified. *Aim:* To investigate the impact of *BRCA1/2* status on women's reproduction and partnering. *Methods:* Data were collected using an online survey with a case-control design from June 2019 to May 2021. Unaffected women aged 18–40 years, who had predictive *BRCA1/2* testing were recruited from eight Australian clinical genetics services. Outcomes included childbearing, relationship status, and intimacy. Descriptive and

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inferential statistics were used. Open text responses were collected, and content analysis was employed. *Results:* 559 participants responded: 62.4% *BRCA* positive; 37.6% *BRCA* negative, with no demographic differences observed between groups. Women were more likely to have children after genetic testing if they were *BRCA* positive (OR 3.5, 95% CI [1.1, 5.6], $p = .03$) and less likely if they had children pretest (*OR* 0.01, 95% CI [0.01, 0.4], $p < .001$). Of the 131 unpartnered participants, 21% described that forming relationships was impacted by the burdensome nature of their *BRCA* status. Intimacy subscales were not associated with *BRCA* status (pleasure $p = .9$; discomfort $p = .9$). However, intimacy (pleasure) was positively associated with body image (*OR* 2.4, 95% CI [1.3, 4.2], $p = .004$). Further, women who had a bilateral prophylactic mastectomy had lower body image than women who had not ($p = .02$). *Conclusion:* Findings from this large multicentre study extend the evidence to develop services better tailored to the needs of younger high-risk women.

ASGC ORAL 2
Reproductive Carrier Screening Participants Want to Know Chance of Having a Deaf Child But Don't Know How They'd Use It

Lucinda Freeman[1,2], Martin Delatycki[3,4], Jackie Leach Scully[5] and Edwin Kirk[1,2,6]

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Background: While many commercial companies include non-syndromic deafness genes in reproductive genetic carrier screening (RGCS) panels, there is little research exploring the acceptability and utility of including these genes. Although some couples have made decisions to avoid having a child who is deaf, there are effective interventions available for children who are deaf, and there is no consensus on whether deafness is a disabling condition. *Aim:* This study explores views of people who have had RCGS regarding inclusion of genes for deafness in expanded carrier screening. *Methods:* Surveys were sent to people who had undergone RCGS three months following receipt of results. *Results:* 930 people were invited to take part, and 278 completed the survey (30% participation rate). When compared to other conditions screened in RGCS, 34% thought deafness was not a severe health condition, 30% thought it was, while 36% were unsure. Most participants (86%) indicated they would want to know their chance of having a child who is deaf. However, only 35% indicated they would make different reproductive decisions if they had an increased chance of having a child who is deaf; 31% said they would not change their reproductive plans and the remainder (34%) were unsure what they would do with this information. *Conclusion:* While the majority of respondents favored screening for deafness, there was no consensus about whether it represents a health condition that warrants changing reproductive decision making. Whether hypothetical views of those who favor it would translate into actual reproductive decision making remains uncertain.

ASGC ORAL 3
'A More Complicated Scenario Than What I Had Ever Realized': Exploring the Experiences of People Who Received an Increased Risk Result for Sex Chromosome Aneuploidy Through NonInvasive Prenatal Testing (NIPT)

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Background: NIPT offers prenatal screening for common chromosome conditions: trisomy 21, trisomy 18, trisomy 13, as well as sex chromosome aneuploidies (SCA). Yet, SCAs have mild and variable features compared to the autosomal aneuploidies for which prenatal screening has been traditionally offered. Little is known about the experiences of people who receive an increased risk SCA result through NIPT. *Aim:* This study aimed to explore the experiences of people who received this result and their perspective on the information, care, and support they received from healthcare practitioners regarding their result. *Methods:* Semistructured interviews were conducted with 18 women and two male partners, who received an increased risk SCA result through NIPT and continued their pregnancy. Transcribed data were analyzed using rigorous thematic analysis to identify important patterns and themes. *Results:* Participants described embarking on NIPT, primarily based on advice from their healthcare professional and without much consideration. Consequently, participants expressed feeling unprepared for the unanticipated complexity of an increased risk SCA result and were faced with making a time-sensitive decision about a condition they had not previously considered. While more pre-test information was desired, timely access to genetic counseling and transparency from clinicians post-test assisted with adjustment to the result. *Conclusion:* These findings suggest that routinization of NIPT may be compromising informed decision-making and resulting in unpreparedness for an increased risk result. Given the likelihood of increasing uptake and expanding the scope of NIPT, resources should be dedicated to educating NIPT providers and ensuring timely access to genetic counseling post-result.

ASGC ORAL 4
Knowledge, Views and Expectations for Cancer Polygenic Risk Testing in Clinical Practice: A Cross-Sectional Survey of Health Professionals

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Background: Polygenic risk scores (PRS) are becoming increasingly available in clinical practice to evaluate cancer risk.

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However, little is known about health professionals' knowledge, attitudes, and expectations of PRS. *Aim:* To explore knowledge, views, and expectations around the use of PRS in clinic for health professionals who provide cancer risk assessments. *Methods:* An online questionnaire was distributed by relevant health professional organizations predominately in Australia, Canada and the US to evaluate health professionals' knowledge, views, and expectations of PRS. Eligible participants were health professionals who provide cancer risk assessments. Results from the questionnaire were analyzed descriptively and content analysis was undertaken of free-text responses. *Results:* In total, 105 health professionals completed the questionnaire (genetic counselors 84%; oncologists 6%; clinical geneticists 4%; other 7%). Although responses differed between countries, most participants (61%) had discussed PRS with patients, 20% had ordered a test, and 14% had returned test results to a patient. Confidence and knowledge around interpreting PRS were low. Although 69% reported that polygenic testing would certainly or likely influence patient care in the future, most felt unprepared for this. If scaled up to the population, 49% expect that general practitioners would have a primary role in the provision of PRS, supported by genetic health professionals. *Conclusions:* These findings will inform the development of resources to support health professionals offering polygenic testing, currently and in the future.

ASGC ORAL 5
Opinions and Experiences of Recontacting Patients: A Survey of Genetic Health Professionals in Australasia

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The issue of recontacting past patients is becoming more relevant, particularly in the familial cancer setting. Next-generation sequencing is providing more information on the pathogenicity and prevalence of genetic variants, often leading to the need to recontact patients. Various international genetic societies have position statements and recommendations to help genetic health professionals (GHPs) navigate the legal, ethical, and practical issues of recontacting. In the absence of a standardized Australasian protocol, we explored the organizational policies, experiences, and opinions of Australasian GHPs regarding patient follow-up and recontacting practices. Forty-five respondents completed an online survey of multiple choice and open-ended questions. The majority of respondents indicated that recontacting occurred on an *ad hoc* basis but most genetic services relied on patients (or family) to initiate the recontact. The idea of implementing a routine recontacting system was widely dismissed by 73% of respondents, citing lack of resources, limited information on legal responsibility, and setting unrealistic expectations as common barriers. However, if recontact were to be initiated, E-communication was believed to be an ideal first step in re-establishing contact with patients. An established position statement or a protocol may help the provision of equitable services, however, patient individuality and circumstances means that a 'one size fits all' approach may not be achievable.

ASGC ORAL 6
Family Communication About Genomic Testing for Early Onset Dementia

Alice Poulton[1,9], Lisette Curnow[2,8], Dhamidhu Eratne[3,4,5] and Adrienne Sexton[6,7]

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Early-onset dementia (EOD) refers to onset <65 years of age and may be associated with genetic cause. Family communication surrounding any genetic risk is complex, and this process may be further complicated in an EOD context due to effects on cognition and behavior, and associated psychosocial consequences. This study aimed to investigate how individuals experience family communication about potential genetic risk and testing for EOD. Thematic analysis was performed on verbatim transcripts of 10 semistructured interviews undertaken with family members who attended a neurogenetics clinic due to a relative diagnosed with EOD. Interviews explored the participants' experiences of learning EOD might be inherited, and the ensuing family communication about genetic testing. Four key themes emerged: (1) a clinical diagnostic odyssey was common and could be a motivator for genomic testing, (2) preexisting family tension and/or disconnection was a common barrier, (3) family members' autonomy was considered, and (4) avoidant coping strategies influenced communication. Communication regarding potential EOD genetic risk is a complicated process, and may be influenced by pre-existing family dynamics, individual coping mechanisms and a desire to promote autonomy in relatives. Findings emphasise the importance of health professionals having awareness of the psychological impact of the clinical diagnostic odyssey and providing appropriate support. To promote effective risk communication, genetic counselors should pre-emptively address family tensions that may emerge in an EOD context and offer psychosocial support to facilitate coping with this tension in an adaptive way. Findings also indicated the importance of extending genetic counseling support to relatives.

ASGC ORAL 7
The Role of Genomics in Diagnosing Inherited Cardiac Diseases

Fergus Stafford[1,3], Neesha Krishnan[1,3], Ebony Richardson[1,3], Charlotte Burns[4,5], Belinda Gray[4,6], Caroline Medi[5], Natalie Nowak[4,5], Hariharan Raju[6], David Richmond[5,6], Mark Ryan[5], Emma S. Singer[4,6], Raymond Sy[5,6], Laura Yeates[1,6], Richard D. Bagnall[4,6], Christopher Semsarian[4,6] and Jodie Ingles[1,6]

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Background: The diagnostic yield of genetic testing for inherited cardiac diseases is ~40%. Many do not meet accepted clinical diagnostic

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criteria, or a genetic diagnosis can indicate a clinical misdiagnosis. For a large proportion, there is growing evidence of a polygenic basis. We sought to evaluate the role of cardiac genomics in clarifying the underlying diagnosis. *Methods:* We performed a retrospective audit of consecutive, unrelated probands attending a specialized, multidisciplinary clinic between 2002-20. Individuals were considered 'solved at baseline', 'solved on review', or 'unsolved', based on reaching a clinical diagnosis and concordant genetic diagnosis. We developed a scoring system to identify those most likely to have monogenic disease, based on phenotype, positive family history, young age at onset and severe presentations (e.g., cardiac arrest, transplant). Scores ≤1.5 indicated low, 1.5-3.0 moderate, and >3.0 a high chance of a monogenic disease. *Results:* There were 1807 probands, with 916 excluded (missing data, no genetic testing). 891 probands were included, with a clinical-genetic diagnosis achieved in 361 (40%) at baseline, 50 (6%) solved on review and 480 (54%) remain unsolved. Diagnostic yield was 32% in the low (n = 533, 60%), 60% in the moderate (n = 177; 20%) and 73% in the high chance of monogenic disease group (n = 181; 20%). Those solved on review were due to: research-based exome/genome sequencing (48; 96%), clinical re-review (18; 36%), new knowledge (19; 38%), segregations (12; 24%) and/or functional studies (5; 10%). *Conclusion:* We highlight an important role of cardiac genomics in clarifying diagnosis and propose a framework for prioritising families with a high likelihood of monogenic disease with the goal to solve their underlying cause of disease.

ASGC ORAL 8
Psychological Wellbeing of Patients and Their Families After Genetic Testing for Dilated Cardiomyopathy

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Background: Genetic testing for individuals with dilated cardiomyopathy (DCM) has become increasingly available; however, there is little research that has assessed the impact of genetic testing on DCM patients' psychosocial wellbeing. *Aim:* This study investigates the psychological impact of genetic testing for DCM and assesses satisfaction and unmet needs. *Methods:* Validated questionnaires were emailed to 167 participants who had received genetic test results for DCM in the past 10 years either through research or through clinical genetic testing. Survey outcomes were coded to a numerical outcome and examined statistically. *Results:* Fifty-three participants responded (response rate 32%) with 33 genotype-positive, 18 genotype negative, and 2 unclear findings (variants of unknown significance or indeterminate results). Motivation for DCM genetic testing was high and was directed primarily by concerns about risk to children and personal health. The overall psychological impact from genetic testing was low and did not differ between participants receiving results within 6 months compared to longer time periods. However, concern about genetic results was significantly higher in the first six months after receiving a genetic test result (p = .0122). Genotype negative respondents showed less tolerance to uncertainty (p = .0396) and had lower trust in their health care providers (p = .0153). *Conclusion:* Genetic testing for DCM was well tolerated and had little overall impact on participants' psychological wellbeing. Participants were highly motivated to access genetic testing and overall satisfaction was high. However, genotype-negative patients may benefit from further support following genetic testing.

ASGC ORAL 9
Preparing Nongenetic Medical Specialists for Genomic Medicine: The Melbourne Genomics Workforce Development Program

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To address the challenge of preparing nongenetic medical specialists for genomic medicine, Melbourne Genomics established a multifaceted workforce development strategy. Informed by adult learning and implementation science theories, this aimed to improve genomic expertise amongst specialists, ranging from basic familiarity to speciality experts. Immersive and structured learning activities (workshops and blended course) were offered and evaluated using mixed methods. All 22 immersive-learning participants completed post-program interviews. 375 specialists participated in structured learning with surveys completed at 4 time-points: baseline (n = 265/375, 71%); post-online modules (blended-learning only, n = 40/85, 47%); post-workshop (n = 277/361, 77%); long-term (>6 month) follow-up (n = 48/291, 16%). Quantitative data were analyzed using descriptive statistics; survey comments and interview data were analyzed using inductive content analysis. Immersive-learning participants reported improved genomic capability and changed genomic medicine practice. They reported being recognized as credible genomic experts within their specialty, acting as a resource for peers and providing speciality expertise to geneticists. Structured learning activities improved participants' self-rated and objective genomic knowledge, skills, and confidence; confidence in knowing referral pathways and demonstrated ability to correctly interpret a report were maintained over time. Structured learning participants reported changes to practice at follow-up (39/48, 81%) including: referring to/consulting Genetics; requesting an exome; educating others. We conclude that structured learning supports long-term improvements in genomic capability, while immersion enables development of speciality genomic experts who, in turn, support peer learning and champion genomics. A workforce development strategy that incorporates both these approaches contributes to sustained behavior change and development of a workforce with a spectrum of genomic expertise.

ASGC ORAL 10
The Evolving Multidisciplinary Delivery of Ultra-Rapid Genomic Sequencing in Acute Care

Fiona Lynch[1,2,3], Belinda McClaren[1,2,3], Amy Nisselle[1,2,3] and Clara Gaff[1,2,3]

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Background: Rapid and ultra-rapid genomic sequencing (rGS) is being established as a first-tier diagnostic test for critically unwell

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infants and children across Australia. This service represents an overlap in practice between the disciplines of genetics and acute care; multidisciplinary teamwork will be crucial for its successful delivery. *Aim:* To explore the evolution of the multidisciplinary delivery of rGS in acute care in Australia. *Methods:* In-depth qualitative interviews were conducted with 11 health professionals with experience in the delivery of rGS: seven genetic counselors (GCs), in 2018 and again in 2020; and four acute care clinicians ('intensivists') at a single timepoint in 2020-21. Interviews were audio-recorded, transcribed and analyzed using content analysis, and compared over time for GCs. *Results:* Interviews reveal an evolving establishment of multidisciplinary practice in acute care. While there were initial challenges, both disciplines appear to be benefiting from workplace learning, facilitating the movement towards truly integrated practice. Intensivists and GCs are working together to support parents' informed decision making about rGS. Irrespective of the outcome of rGS, participants report that families need post-test support for a variety of reasons. *Conclusion:* This study demonstrates maturation in the delivery of rGS over recent years and provides insight into the future delivery of genomic medicine in acute care. Practices reported around decision making are still putting undue pressure on parents to consent to rGS. A wider range of post-test needs were reported by health professionals than families undergoing rGS, making all perspectives essential for informing service delivery.

ASGC ORAL 11
Outcomes of a Four-Year Laboratory-Based Genetic Counseling Role

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The Royal Children's Hospital (RCH) has employed a laboratory-based genetic counselor (LBGC) since mid-2017. The LBGC aims to facilitate access to high-quality, cost-effective, clinically indicated genetic and genomic testing hospital wide. This is achieved by overseeing the test request review process and providing ongoing education and support to nongenetics clinicians within the hospital. Data collected via hospital systems as well as a LBGC-designed REDCap database allowed for evaluation of the role. Analysis showed the number of referral laboratories decreased dramatically over the initial 3 year period, from >100 referral laboratories in 2015, to <30 in 2020. This is despite a steady increase in test requests being observed, with orders increasing by 52% from 2017-2020. The LBGC role enabled management of the increased test requests in a financially sustainable way, where identification of and access to alternative funding sources for appropriate requests represented a 62% cost saving for RCH in 2018/2019. As test requests continue to increase and more genomic tests become available, the number of declined or modified requests are expected to rise from an average of 9%. A monthly genetic review meeting allowed for strong relationships to be built with frequent test requestors as well as the implementation of specific processes for expert reviewers in different departments. Although departmental ordering trends and diagnostic yield improved, ultimately the review process confirmed that nongenetics clinicians would benefit from the ongoing support of this role. The role continues to be supported by a clinical geneticist and a recently employed laboratory medical technician.

ASGC ORAL 12
Patient Perspectives and Experience with Pharmacogenomics Testing: A Retrospective Review on Clinical Utilities

Andrew Tjokrowidjaja[1], Rosalind Moxham[2], Sing Nguyen[3], Darren Roberts[4,5] and Kathy Wu[2,3,4,6]

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Background: Pharmacogenomics is underutilized in Australia. Understanding the perspectives of patients who had undergone pharmacogenomics testing will help inform wider implementation of pharmacogenomics into Australian healthcare. *Aim:* To investigate the potential utility of pharmacogenomics and to assess patient experience, understanding and usage of pharmacogenomics results. *Methods:* A retrospective audit of pharmacogenomics results of approximately 100 patients who had undergone testing at St Vincent's Clinical Genomics (SVCG) from 1st of July 2018 to present was performed. Data on patient experience, understanding and usage of pharmacogenomics were collected via an electronic survey created on Research Electronic Data Capture (REDCap). Bar charts and percentages were used to summarize categorical data. *Results:* To date, 87 patients (age range: 18-73, 47 female and 40 male) were referred to SVCG for pharmacogenomics testing. Of these, 74 patients have received their pharmacogenomics results. Of these 74 patients, 12 patients (16.2%) were on medications with a high risk of drug-gene interactions (DGIs) and 43 patients (58.1%) were on medications with a moderate risk of DGIs. Sixty-three patients have been invited to participate in the survey to date with a response rate of 23.8%. Preliminary survey results showed 87% of respondents understood their pharmacogenomics results; 53% of respondents did not have their medications changed following testing; and there were mixed responses on the perceived utility of pharmacogenomics. *Conclusion:* A significant proportion of patients were taking at least one medication with a high- or moderate-risk DGI. Patient-perceived utility of pharmacogenomics was mixed, although most were able to understand their results.

ASDG SIG MEETING

INVITED SPEAKER
UCSC Genome Browser — The Latest Developments

Robert M. Kuhn

University of California Santa Cruz, CA, USA

The UCSC Genome Browser has been offering genomic annotations on the human and other genomes for more than 20 years. As the types of experimental data annotating the genome have grown, so has Browser capability. More data and more display types mean more complexity. With too many innovations to present in a short time, this presentation will focus on a new feature, Recommended Track Sets, designed to simplify configuration of the Browser in the clinical setting, offering relevant tracks for interpretation of variants at either single-nucleotide (SNV) or copy-number (CNV) scale. In the process, we will explore the new beads-on-a-string display for the five classifications of ClinVar data (P, LP, VUS, LB, B), which

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shows at a glance for each variant the number of reports in each category, with the specifics of each one click away. There are a number of other changes to these tracks that make the data more useful. Other new features will be presented as time allows.

SELECTED ORALS

Is it Cytogenetic or Molecular? The Challenges of Convergence Between Traditionally Separate Disciplines

Sebastian Lunke[1,2,3], Anna Ritchie[1], Amber Boys[1], David Francis[1], Belinda Chong[1], Maria Kaps[1], Naomi Baker[1] and Meaghan Wall[1,2,3]

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Textbooks teach us that cytogenetic techniques detect large, chromosome level variants, while molecular genetics investigates single nucleotide changes and small insertion/deletion events. There was a gap between the smallest events detected by cytogenetics and the largest events detected by molecular genetics, representing a persistent blind spot for genetic pathology. However, resolution of SNP-based microarrays has recently increased to a level where intra-genic variants as small as single exon deletions can now be routinely detected, while genomic technologies are increasingly used for highly robust copy-number variant calling. Accordingly, the traditional detection gap that divided cytogenetic and molecular disciplines has been quietly closed. Simultaneously, approaches to variant curation and interpretation have evolved, with separate ACMG guidelines for cytogenetic and molecular disciplines now available as reference standards. Inadvertently, we find ourselves in a situation where the same variant in the same case is interpreted differently depending on whether it is identified in a cytogenic or molecular laboratory, with expert analysts from neither discipline being entirely comfortable in interpreting variants that fall into the previous size gap. We will share the challenges encountered by our laboratory during this transition, exemplify areas of inconsistency, and present approaches and recommendations aimed at establishing a consistent interpretation approach between the disciplines.

Variantgrid 3.0: A Web-Based Software Solution for Genomic Analysis and Variant Curation

Sarah L. King[1,3], David Lawrence[1,3,4], James Andrews[1,3], Julien Soubrier[1,2], Song Gao[1], Jinghua Feng[3,4], Rob King[1,3,4], Wendy Parker[1,3], Joel Geoghegan[5], Anna L. Brown[1,3], Hamish S. Scott[1,3,4,6], Karin S. Kassahn[1,3] and Andreas W. Schreiber[2,3,4]

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Background: In recent years, genomic sequencing has evolved from a promising research tool to a mainstay of Australian clinical care. Despite these advances, there remains a significant bottleneck in access to training solutions and genomics analysis software for non-bioinformaticians. *Aim:* To provide a clinical-grade analysis platform for Australian researchers and clinicians to perform genomic interpretation and variant curation. *Method:* Over the last 8 years. we have built a web-based tool, VariantGrid, that enables versatile genomescale analysis of both somatic and germline variants by non-bioinformaticians. We report here on the release of a substantially updated version, VariantGrid 3.0 (https://variantgrid.com), and its associated online training program (https://variantgrid.moodlecloud.com/). *Results:* VariantGrid 3.0 represents a significant advance on previous releases including support for parallel hg19 and hg38 analysis available with both Ensembl and Refseq transcripts; full variant annotation including gnomAD V3, SpliceAI, REVEL, and MasterMind; advanced phenotype-driven analysis using MONDO, OMIM, HPO ontologies; live integration of PanelApp and ClinGen gene curation databases; compatibility with REDCap research software, and the addition of a variant curation and reporting module aligned to ACMG and ClinGen recommendations. Further, the release of accompanying online training modules provides an efficient means of introducing new users to genomics analysis and variant curation using publicly available data. *Conclusion:* VariantGrid 3.0 is a flexible genomics analysis platform available to support the continued development of the genomics community.

Abnormal Initiation of Transcription: An Important Consideration for RNA Analysis Of Intron-1 Donor Splice Site Variants

Adam M. Bournazos[1,2], Shobhana Bommireddipalli[1], Caitlin Edwards[3], Aamira J Huq[4,5], Bryony A Thompson[6,7], Karin van Spaendonck-Zwarts[8] and Sandra T Cooper[1,2,9]

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Background: Transcription and pre-mRNA splicing are closely coordinated through interplay between the transcription machinery and spliceosome. The U1 small nuclear ribonucleoprotein (snRNP), a core component of the spliceosome that recognizes the donor splice site, is required for efficient transcription elongation through intron-1. Here we present two novels variants of uncertain significance (VUS) in *NF1* (NM_000267.3:c.59A>C) and *PRPH2* (NM_000322.4:c.581+5G>A) affecting the intron-1 donor that result in abnormal initiation of transcription. *Methods:* Reverse transcriptase polymerase chain reaction (RT-PCR) was performed using RNA from patient blood or skin fibroblasts. Amplicons were gel-extracted and analyzed by Sanger sequencing. *Results:* In both cases, RT-PCR indicated that transcription initiates at an ectopic start site between our exon-1 and exon-2 forward primers, removing the encoded start methionine. A distal heterozygous coding variant used to demarcate each allele showed correctly spliced transcripts containing exon-1 were expressed from a single allele. RNA analysis enabled reclassification of c.581+5G>A from VUS to pathogenic while c.59A>C remained VUS. *Conclusion:* Intron-1 donor variants can lead to abnormal transcription initiation, likely due to loss of U1 snRNP recruitment preventing crosstalk with the transcription machinery. Activation of an ectopic transcription start site may not result in any novel splice junctions and go undetected by splicing assays. Furthermore, a distal heterozygous coding variant was crucial to show the loss of correctly spliced transcripts containing exon-1. Approaches with sufficient read length to encompass a distal variant,

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are best suited to phasing transcripts. Hence, abnormal initiation of transcription is an important consideration for RNA analysis of intron-1 donor variants.

Transitioning Diagnostic Genomics to HG38

Julien Soubrier[1,2], Song Gao[1], Jinghua Feng[3,4], David Lawrence[1,3], James Andrews[1,3], Sarah King-Smith[1,3], Rob King[1,3], Wendy Parker[1,3], Anna L. Brown[1,3], Hamish S. Scott[1,3], Andreas W. Schreiber[2,3,4] and Karin S. Kassahn[1,3]

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Background: The hg38 human genome reference assembly was released in 2013, but is yet to be adopted by most diagnostics and research laboratories. *Aim:* We sought to update our Next Generation Sequencing workflows to hg38 and validate them for clinical application. *Methods:* We have re-coded our bioinformatics pipelines using a workflow management system (Snakemake), settled on a specific hg38 version, updated third party tools and annotation sources, and implemented retrocompatibility to allow switching between hg19 and hg38. We used our in-house VariantGrid interpretation tool to perform extensive testing on the resulting variants, using in-house and reference data sets. *Results:* We successfully harmonized research and clinical bioinformatics pipelines into a single framework. Improved workflow management has led to significant reduction in compute times, while sensitivity and specificity estimates were comparable to those for hg19. We tested and verified all critical analytical, annotation, and interpretation steps, which helped identify issues entailing potential clinical risk, such as changes to gene symbols and reference transcripts across annotation versions, or imperfect variant lift-over between assemblies limiting comparisons for validation purposes. Also, a number of clinically significant target regions are no longer unique in hg38 due to paralogous sequence not being present in hg19. *Conclusion:* Although transitioning to hg38 requires significant resources, it provides an opportunity to optimize genomics analyses, while mitigating the increasing risk of using outdated reference, tools, and annotations. The lessons learnt by our laboratory may be helpful to others embarking on a similar journey, whether using in-house or commercial tools.

A Robust Method for Detecting Contamination in Germline NGS Data

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Background: Contamination between DNA samples, whereby some amount of data associated to a sample comes from a source other than the expected individual, presents a significant threat to accurate variant detection. Therefore, there is a need to be able to confidently detect contamination when it occurs. However, detection of low level contamination can be masked by other quality issues. Therefore a highly robust and reliable method is needed that is both sensitive and specific. One approach is to examine variant allele frequencies (the proportion of reads supporting each variant). In a pure diploid sample, heterozygous alleles should be approximately equally balanced and homozygous alleles should be represented in 100% of the observed reads. However, allele frequencies in contaminated samples will deviate from these values. *Methods:* Using both simulated and real examples of sample contamination, we evaluated and compared three established methods of contamination detection based on variant allele frequencies. *Results:* All measures produced inflated scores when contamination occurred; however, we found that for some data types, these metrics were unable to clearly distinguish contaminated samples when other quality issues occurred. Based on these results, we developed a new method, termed the 'upper VAF outlier check'. By focusing on specific variant types and high confidence upper portions of the allele fraction distribution, this method confidently identifies contamination in samples containing as little as 5% foreign material. *Conclusion:* Methods for contamination detection can be compromised by other quality issues, however our improved method is robust to these issues while maintaining sensitivity.

Transcript Variants of Genes Involved in Neurodegeneration are Differentially Regulated by the APOE And MAPT Haplotypes

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Background: Genetic variations at the Apolipoprotein E (ApoE) and microtubule-associated protein tau (MAPT) loci have been implicated in neurogenerative diseases, but their exact molecular mechanisms are unclear. *Aim:* The aim of our study was to identify the genes regulated by the variations in the ApoE and MAPT locus in order to provide the explanation for the ApoE and MAPT genetic effects. *Methods:* Transcript level linear modelling of the blood whole transcriptome data (RNA-seq) and genotypes of the 570 subjects in the Parkinson's progression markers initiative (PPMI) cohort. ApoE, MAPT haplotypes, and two SNPs at the SNCA locus (rs356181, rs3910105) were used to detect expression quantitative trait loci (eQTLs) associated with the changes in the transcriptome and differential usage of transcript isoforms. *Results:* We identified 151 genes associated with the genotypic variations, 29 *cis* and 122 *trans* eQTL positions. ApoE e4 haplotype has profound effect on the expression of TOMM40 transcripts. This finding explains the frequently established genetic association with the APOE e4 haplotypes in neurodegenerative diseases. MAPT haplotypes had a significant differential impact on 23 transcripts from the 17q21.31 and 17q24.1 loci with the largest up-regulating ($\beta = 256$) and the largest downregulating ($\beta = -178$) effect sizes on two different transcripts of the same gene (LRRC37A2). Intronic SNP in the SNCA gene, rs3910105, differentially induced expression of three SNCA isoforms. *Conclusion:* In conclusion, this study established that APOE e4 and MAPT H1/H2 haplotypic variants significantly regulate the expression of several genes related to the neurodegeneration.

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Investigation of Mitochondrial Variants Identifies a Link Between Cerebral Small Vessel Disease and Alzheimer's Disease

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Background: Cerebral small vessel diseases (CSVDs) are known to cause strokes, migraine, and dementia phenotypes. Mutations in both nuclear DNA (*NOTCH3, COL4A1, COL4A2, TREX, GLA*) and mitochondrial DNA have been found to cause monogenic forms of CSVD such as CADASIL and mitochondrial encephalopathy with lactic acidosis and stokes (MELAS). Despite a known mitochondrial link to CSVD, there is a gap in the literature regarding mutations in the mitochondrial genome causative of other CSVD phenotypes. *Aim:* The aim of this study was to investigate mutations in the mitochondrial genome as well as nuclear encoded mitochondrial proteins (NEMPs) in a identify a link between the mitochondria and CSVD pathology. *Methods:* NEMP mutations were extracted from whole exome sequencing (WES) data from 50 *NOTCH3* negative CADASIL patients. Mitochondrial sequencing (MitoSeq) was completed on the same cohort using an in-house developed protocol and reads were aligned to the Cambridge reference sequence (rCRS). A mixture of *in silico* pathogenicity tools and population databases were utilized to identify causative mutations in both the MitoSeq and targeted WES data. *Results:* Candidate mutations were identified with links to MELAS, encephalopathy, and Alzheimer's disease-related phenotypes. From these mutations, those that were within *POLG, MTO1, LONP1, NDUFAF6, NDUFB3,* and *TCIRG1* appear most likely to play a role in CSVD or Alzheimer's disease pathology. *Conclusion:* The exploration of the mitochondrial genome in conjunction with the NEMP genes identified a potential link between CSVD and Alzheimer's disease.

MDFIC Mutations Cause Autosomal Recessive Central Conducting Lymphatic Anomaly (CCLA)

Saba Montazaribarforoushi[2,*], Alicia B. Byrne[1,*], Jan Kazenwadel[1,*], Drew L. Sutton[1,*], Pascal Brouillard[3,*], Genevieve A. Secker[1], Peer Arts[1], Milena Babic[4], Kelly L. Betterman[1], Peter Brautigan[4], Paul Thomas[2], Christopher N. Hahn[2,4,5], Eric Haan[6], Denise Adams[7], Ariana Kariminejad[8], Laurence Boon[3,9], Nicole Revencu[9,10], Raphael Helaers[3], Christopher Barnett[11], Lynette Moore[11], Miikka Vikkula[3,9,12,#], Natasha L. Harvey[1] and Hamish S. Scott[1,2,4,5]

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Background: Central conducting lymphatic anomaly (CCLA), characterized by the dysfunction of core collecting lymphatic vessels including the thoracic duct and cisterna chyli often manifests as non-immune hydrops fetalis (NIHF). Clinical presentation of CCLA also includes chylothorax, pleural effusions, chylous ascites or lymphoedema, and often results in fetal or perinatal demise. While mutations in RAS/MAPK signalling pathway components have been documented in some patients with CCLA, the genetic etiology of lymphatic anomalies remains uncharacteristic in the majority of cases[1]. *Methods/Results:* Here, by exploring the genetics underlying stillbirth as part of Genomic Autopsy Study, we identified five patients in whom compound heterozygous mutations in *MDFIC*, encoding the MyoD family inhibitor domain-containing protein, were documented. Two fetuses presented with NIHF, pleural and pericardial effusions and lymphoedema and three children from three independent families with a history of hydrops fetalis followed by postnatal lymphoedema, unexplained fever episodes, and inflammation. Generation of a mouse model of the human *MDFIC* truncating mutation (Met131fs*) revealed that homozygous mutant mice died perinatally exhibiting chylothorax, the accumulation of lipid rich chyle in the thoracic cavity. The lymphatic vasculature of homozygous *Mdfic* mutant mice was profoundly mis-patterned, particularly in the diaphragm and thoracic wall and exhibited defects in lymphatic vessel valve development. *Conclusion:* Mechanistically, we demonstrate that the biallelic variants in *MDFIC* lead to CCLA and cysteine-rich C-terminus of MDFIC, which is absent in the MDFIC Met131fs* truncated protein, is essential for interaction with GATA2, a transcription factor with an essential role in lymphatic vessel valve development.

Validation of a Targeted Next Generation Sequencing Panel for Molecular Diagnostics of Hematological Neoplasms

Wendy T. Parker[1,2], Julien Soubrier[1,3], Song Gao[1], David Lawrence[2,4], Jinghua Feng[2,4], Karen L. Ambler[1], Adrian Purins[1], Sarah L. King-Smith[1,2], Rosalie R. Kenyon[2,4], Ming Lin[2,4], Rob King[2,4], Hamish S. Scott[1,2,4], David M. Ross[5], Andreas W. Schreiber[2,4], Karin S Kassahn[1,2] and Anna L. Brown[1,2]

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Somatic mutation detection using next-generation sequencing (NGS) is recommended for accurate diagnosis, prognostication, and therapy selection for patients with hematological neoplasms. SA Pathology has offered NATA-accredited NGS for myeloid neoplasms since 2019, utilizing a custom Roche SeqCap EZ capture panel targeting the full coding region of 41 genes (0.1 Mb). The Myeloid Panel was designed for myeloproliferative neoplasms (MPN), myelodysplastic syndromes, acute myeloid leukemia, and therapy-related myeloid neoplasms. We recently redesigned our sequencing panel to broaden the scope of testing to also include somatic mutation hotspot regions important for some lymphoid malignancies and triple negative MPN (TN-MPN). The new IDT xGen Custom Hyb Panel covers 21 full genes, selected exons of a further 25 genes, and common SNPs on chromosomes 9 and 17 for simultaneous LOH analysis (0.07 Mb). The new Hematology Panel has enhanced coverage uniformity and the smaller target region has allowed for batch size increases by 50%, while maintaining similar mean coverage (>1000X) using a MiSeq instrument. Updates to our in-house bioinformatics pipeline, including switch to the hg38 reference genome and Vardict and Mutect2 somatic variant callers,

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and our custom variant curation software VariantGrid, have further improved performance. Internal tandem duplication variants in FLT3 are difficult to detect by NGS and were not called in our previous panel. These are now detectable down to <1% VAF. The Hematology Panel enables accurate and sensitive NGS testing of patients with myeloid neoplasms, myeloma, lymphoma, chronic lymphocytic leukemia and TN-MPN, which may improve outcomes for cancer patients in SA.

ASGC SIG MEETING

INVITED SPEAKER
Psychological Counseling Theories Can Inform Genetic Counseling

Barbara B. Biesecker

RTI International, Maryland, USA

Genetic counseling largely entails conveying scientific information to patients to make informed decisions. Evidence suggests genetic counselors prioritize information provision. Importantly, the work also involves psychological suffering. Patients who are affected or at risk for serious illness, parents whose children have rare disorders, and couples who lose an affected fetus experience sadness, disappointment, loss of control, and grief. A genetic counselor can play an instrumental role in their clients' healing processes. Psychological counseling theories, such as cognitive behavioral and patient-centered theories, provide frameworks for this casework. While theories are applied in accordance with clients' needs, it is the *common factors* across theories that lead to a therapeutic alliance to promote patient wellbeing. These factors include goal alliance, empathy, genuineness, positive regard, and facilitating mastery. Genetic counselors use goal alliance and facilitating mastery regularly in cases that focus primarily on providing information for decision making. Further, genetic counselors often have empathic and genuine characters—these traits having drawn them to the professional work. As such, the opportunity to expand one's skills to include routinely establishing a therapeutic alliance with a goal to reduce suffering is within reach. In this session, opportunities to incorporate a theoretical framework and common factors of psychological counseling into genetic counseling will be presented within a discussion of case examples where they have been put into practice.

INVITED SPEAKER
Are Australasian Genetic Counselors Ready to Deliver Behavior Change?

Chris Jacobs[1], Erin Turbitt[1], Alison McEwen[1] and Lou Atkins[2]

[1]Graduate School of Health, University of Technology Sydney, NSW, Australia and [2]Centre for Behaviour Change, University College London, UK

Background: Completion of the human genome project promised a transformation in health prevention. Despite clients' oft-cited motivation for genetic testing being to change health behavior, there is little evidence that receiving genetic test results leads to behavior change. To effectively change behavior requires a theory-driven coordinated set of activities (i.e., behavior change techniques BCTs). Genetic counselors (GC) are ideally positioned to facilitate behavior change, yet the extent to which BCTs are applied is unclear. *Aim:* To explore Australasian GCs' perception and readiness for behavior change to inform an intervention to facilitate the delivery of BCTs. *Methods:* Participants were recruited via the Australasian Society of Genetic Counselors (ASGC). Five online focus groups and one online interview were conducted with 26 GCs who completed their training more/less than 10 years ago. Verbatim transcripts were analyzed using thematic analysis and mapped to the COM-B model. *Results:* Three client behavioral outcomes of genetic counseling were identified: attend recommended screening/heath appointments, access relevant information, and support, and share accurate information with relevant family members. The influencers and barriers to GCs' delivery of BCTs, the strategies needed to facilitate behavior change, and the influencers and barriers to clients' behavior change were identified. Some BCTs were evident, including providing information and encouraging self-management. There were gaps in GCs'/clients' capabilities, opportunities, and motivations to deliver BCTs/change health behaviors. *Conclusion:* Although some BCTs are evident in practice, enhancing awareness and knowledge of behavior change theories and strategies will assist GCs in effectively changing clients' health behavior.

INTERESTING CASES
Unexpected Results With Devastating Consequences

Emma Creed

Mercy Hospital for Women, Melbourne, VIC, Australia

Sara*, a 32-year-old G2P1, was referred for prenatal genetic counseling in early pregnancy, as her –year-old son was diagnosed with a de novo pathogenic variant in the X-linked *CASK* gene which caused epilepsy and developmental delay. Sara was given a low recurrence risk but elected to undergo chorionic villus sampling (CVS) in her current pregnancy for reassurance. CVS results showed the pregnancy had inherited the pathogenic variant in the *CASK* gene AND a de novo 7q11.23 microduplication. Sara elected a termination of pregnancy (TOP). This case raised a number of issues and challenges including dealing with unexpected results, economic, and social implications of the COVID pandemic restrictions, feelings of guilt associated with TOP, and re-evaluation of the chances of having a healthy child. My reflections will focus on the experience of receiving complex findings under the constraints of a global pandemic, which contributed to the devastation this couple experienced. *Pseudonym.

Li-Fraumeni Syndrome, Privacy and Narrative Practice: A Case of Unexpected Findings Following Genetic Testing in a Deceased Relative

Giulia Valente

Austin Health, Melbourne, VIC, Australia

Hattie (33y) was referred for risk assessment to inform surgical planning for a breast reduction. Her mother had multiple cancers, including breast cancer, before passing away at age 49. As her mother was very private, Hattie had limited knowledge. Testing her mother's stored DNA identified a pathogenic *TP53* variant. Hattie had anxiety and depression related to her mother's death. Hattie spoke of her cancer anxiety, how her mother's decision not to speak openly about her cancer history had fractured family relationships and how her relatives had developed theories about why her mother had developed cancer. The identification of the *TP53* variant helped Hattie to address some of her unresolved emotions towards her mother, including blame linked to these 'cancer theories'. While undergoing predictive testing, Hattie faced anxiety, impacts of COVID-19, job loss, and marital breakdown. This case demonstrated complex

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psychosocial issues and implementation of advanced counseling skills including narrative practice.

Genetic Syndromes and Eligibility for Organ Transplant: A Case Study

Cass Hoskins

Peter MacCallum Cancer Centre and the Royal Melbourne Hospital, Melbourne, VIC, Australia

How genetic information influences the management of affected individuals is an important aspect for genetic health professionals and patients alike, particularly as genetic testing continues to move into precision medicine. On rare occasions, this includes decisions surrounding eligibility for organ transplantation. Given the relative scarcity of organs, clinicians must assess and ultimately decide which patients will have access to organ transplantation as a therapy. Such decisions are balanced between the conflicting ethical principles of equity and utility, weighing up equal opportunity against deriving the maximum possible benefit from the limited number of organs available for transplantation. This interesting case details the ethical considerations generated by one family's experience with genetic testing for TP53 (Li-Fraumeni syndrome) and subsequent eligibility, or ineligibility, for organ transplant. I will present the various clinical aspects, psychosocial implications, and family dynamics associated with this case to demonstrate the increasing implications of genetics in today's medicine.

Genetic Counseling in the Era of Genomewide Noninvasive Prenatal Testing: Balancing Clinical Utility and Parental Uncertainty

Joanne Kelley

Mercy Hospital for Women, Melbourne, VIC, Australia

Noninvasive prenatal testing (NIPT) is a superior screen for common aneuploidy, associated with high positive predictive values (PPVs) and well-defined causes of false-positive results. Despite proven clinical utility for carriers of balanced translocations in pregnancy, the benefit of offering genome-wide NIPT (GW NIPT) for the general pregnant population is considerably less certain. The finding of an increased risk for a random autosomal trisomy (RAT), segmental aneuploidy, or copy number variant (CNV), often associated with a low PPV, can result in months-long investigations for parents with accompanying stressors and uncertainty. Although helping parents manage uncertainty is a familiar role for genetic counselors, these findings present some unique challenges that have prompted reflection of, and implications for, practice. Considering both the 'science and art' of genetic counseling[1] practice and using case studies to illustrate, I reflect on our experience and learnings when helping parents manage increased risk results from GW NIPT.

'I'm a Man': Heteronormative Views and the Potential Impact of a Visibly LGBTIQA+ Inclusive Workplace on a Genetic Counseling Appointment

Joshua Schultz

Parkville Familial Cancer and Genomic Medicine, Melbourne, VIC, Australia

In recent years, there has been an increased research focus in regards to healthcare provided to the LGBTIQA+ community to ensure equality of care, with the data highlighting the importance of creating a visibly safe and inclusive environment for patients. This case study examines the counseling issues that emerged from a challenging appointment with a male patient who attended a BRCA2 predictive testing discussion, and eventually declined genetic testing. In particular, this case will explore the strong religious and heteronormative views of the patient, as well as the ability of the genetic counselor to remain patient-centred and overcome countertransference. While it was not explicitly stated that the patient disagreed with the inclusive views of the department, this case will reflect on how a visible display of inclusivity for LGBTIQA+ individuals in the service may impact a genetic counseling appointment.

'I Feared Deportation': A Refugee's Story of Surviving Breast Cancer and the Impact on Genetic Counseling

Joanne Isbister-Smith

Genomic Medicine & Familial Cancer, Melbourne, VIC, Australia

Many of Australia's refugees from Myanmar (Burma) came from the Karen State feeling conflict or persecution. Prior to resettling in Australia, many refugees spent time in refugee camps in Thailand. Thailand is not a signatory to the 1951 Refugee Convention, and therefore does not recognize refugees under domestic laws. Refugees are at constant risk of deportation, and lack access to employment, education, and healthcare. Subsequently, refugees often present with advanced-stage disease and suffer significant complications. This case study examines the unique counseling issues that emerged from an appointment with a refugee diagnosed with metastatic breast cancer. This case will reflect on the cross-cultural counseling skills utilized by the genetic counselor to explore the clients' narrative to elicit cultural expectations, attitudes, and health belief practices, while supporting autonomous decision-making around genetic testing. In particular, this case highlights the importance of understanding the specific needs and experiences of our refugee patients.

The Eye of the Dystonic Storm — The Emotional Impact of a Rare, Life-Limiting Neurological Condition

Jessica Taylor and Joshua Schultz

Genomic Medicine Department, The Royal Melbourne Hospital, Melbourne, VIC, Australia

Counseling for neurogenetic conditions poses unique challenges due to the potential for rare, progressive, and often complex phenotypes in many individuals. This case study examines the impact of working with patients who have rare life-limiting conditions and their families. Sarah*, a young woman found to have a specific *ACTB* pathogenic variant causing early-onset dystonia and deafness, died suddenly and tragically while our service was facilitating whole exome sequencing and segregation testing. We will explore the complex grief expressed by Sarah's mother around having a child with this condition and the impact of Sarah's death on both the mother and counselor. In particular, the counselor will reflect on their own emotional response and the feeling of 'Could I have done more?'. It will also examine the case from an interesting genetics perspective regarding the rare complication of a dystonic storm and the impact this had on the family. *Pseudonym used.

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Two for One, in More Ways Than One

Kirsten Boggs

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The concept of nondisclosure within families in the field of genetics is not new; however, when a mother attends an appointment alone regarding results for her child and makes a decision not to tell anyone else in the family, including her husband—how do we move this forward? This case involves two siblings, Benji* and Joel*, who were both diagnosed with dilated cardiomyopathy (DCM) in their first year of life. I first met their mother when Joel was admitted to the Paediatric Intensive Care Unit, where he was enrolled in the Acute Care project. Rapid trio whole exome sequencing did not identify the cause of this condition. His brother, Benji, was born some months later, and was diagnosed early on with DCM. Quad whole genome sequencing was arranged, which not only identified the genetic cause for the brothers' cardiac condition but also identified a significant secondary finding. Discussion of this case will include a summary of the literature surrounding implications of nondisclosure, and that of the reporting of incidental findings in this context. The ethical considerations around genetic results and who owns the information will also be explored. *Pseudonyms used.

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