

## Abstracts

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

## Poster Presentations

### CLINICAL GENETICS

#### ACT Genetic Service Approach to ‘Rebooting’ Cancer Genetic Testing Wait Times After COVID-19

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**Background:** The ACT Genetic Service acquired funding under Operation Reboot, a \$3.5-million initiative developed by Canberra Health Services to address increased wait times due to COVID-19. This funding was used to employ an Associate Genetic Counselor for 8 weeks with the objectives to: (1) see 100% of CAT1 patients in 30 days, (2) see 90% of CAT2 patients in 90 days, and (3) reduce CAT3 referrals by 40% of June 2020 numbers. **Aims:** To analyze the effectiveness of our approach to Operation Reboot. **Methods:** Waiting times for cancer genetic testing at the ACT Genetic Service were extracted from November 2019 to March 2021, and descriptive statistics were used to analyze the data. For the purpose of analysis, ‘COVID’ refers to April 2020–November 2020, ‘OpReboot’ refers to December 2020–January 2021 and ‘Post-OpReboot’ refers to February 2021–March 2021. **Results:** The average number of patients seen per month increased by 144% during Operation Reboot (COVID: 10 patients; OpReboot: 26 patients). The intervention decreased average CAT1 and CAT2 wait times by 63% (COVID: 2.4 months; Post-OpReboot: 0.9 months) and 28%, respectively (COVID: 2 months; Post-OpReboot: 1.5 months). The CAT3 average wait times increased by 53% of June 2020 numbers from 8.0 to 12.2 months in the post-OpReboot period. **Conclusion:** The objectives for both CAT1 and CAT2 referrals were met as a result of Operation Reboot. The CAT3 objective was not met although this intervention may allow for increased opportunity for this to be addressed in future.

#### Heterogeneity in How Women Value Risk-Stratified Breast Screening

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**Background:** Risk-stratified screening has potential to improve benefit-to-harm ratios of population breast cancer (BC) screening

programs. We hypothesize a person-centered approach to implementation will optimize participation rates. **Aim:** To explore what women would value when deciding to participate in a risk-stratified breast screening program by having a personal BC risk assessment, and the relative impact of each factor on their decision. **Methods:** Women across the BC risk spectrum were recruited through the *LifePool* study and Parkville Familial Cancer Centre. Multicriteria decision analysis was used to determine the relative weights and level preferences of eight criteria women reported would influence their decision to participate in a personal BC risk assessment. Latent preference heterogeneity was explored through cluster analysis. **Results:** Of 363 women surveyed, 95% would accept a personal BC risk assessment. The two criteria most highly valued by participants related to program access, ‘accessing information’ and ‘testing process’, both of which significantly influenced participation ( $p < .001$ ). 73% preferred information by letter/online. Storage of genomic data had less impact than expected ( $p < .001$ ). Four latent preference-based subgroups were identified. Women in the largest subgroup focussed on program access, with membership predicted by low educational attainment. Higher relative perceived breast cancer risk predicted membership of the smallest subgroup who valued test parameters: ‘scope of test’ and ‘test specificity’. **Discussion/Conclusion:** These findings suggest that a population-based BC risk assessment framework may be socially acceptable. When implementing a breast screening program tailored to personal risk, these findings suggest population acceptance and participation can be maximized through tailoring implementation to population preference-based subgroups.

#### Expanding the POT1 Tumor Predisposition Syndrome

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**Background:** ‘Protection of telomeres 1’ (POT1) binds to telomeres to shield them from excessive degradation or lengthening. Pathogenic variants in *POT1* result in a tumor predisposition syndrome (POT1-TPDS) which includes susceptibility to angiosarcoma, chronic lymphocytic leukemia, colorectal cancer, cutaneous melanoma

(CM) and glioma. Here, we expand the spectrum of cancers to include uveal melanoma (UM) and a range of hematological malignancies. *Aim:* The aim of this study was to identify the genetic cause of disease predisposition in high-risk CM and UM families, and to conduct functional evaluation of candidate susceptibility variants. *Methods:* Patients ( $n = 461$ ) were recruited from Queensland, and DNA samples were collected to be sent for next generation sequencing. Telomere length assays were done for functional characterization of *POT1* variants. *Results:* Three variants, c.281\_282del, c.1458\_1459del, and c.670G>A in *POT1* were identified. The two loss-of-function variant carriers had both CM and UM, and functional characterization showed carriers had longer telomeres, compared to age-matched healthy controls. Currently classified as a VUS in ClinVar, missense variant c.670G>A was identified in a family with CM and hematological malignancies not yet associated with the *POT1*-TPDS, including follicular lymphoma and chronic myeloid leukemia. Functional assessment has previously shown c.670G>A to disrupt *POT1* binding, leading to longer, more fragile telomeres. *Conclusion:* The genetic basis of cancer susceptibility in three families from our study was found to be caused by pathogenic variants in *POT1*. Our findings indicate that pathogenic variants in *POT1* predispose to a wide range of tumor types, having broader implications for genetic testing, screening, and counseling recommendations.

### Not So Fast: Why Somatic Testing in Cancer Patients Doesn't Tell the Whole Story

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*Background:* Both germline and somatic genetic testing are well-established tools for precision medicine in cancer patients. Sequencing of a tumor detects somatic variants which can be used to inform therapy and can also detect germline variants, but with important limitations. As such, these tests can fail to report clinically actionable germline events. *Methods:* We retrospectively analyzed a cohort of 2023 cancer patients with previous tumor sequencing results who were receiving germline testing for cancer predisposition genes. Indications for germline testing included: tumor findings of potential germline origin, treatment guidance or surgical planning, and personal/family history. High and moderate risk pathogenic and likely pathogenic germline variants (PGVs) were analyzed. *Results:* Overall, 30.5% ( $n = 617$ ) of patients harbored a PGV, most of which could have treatment implications. PGVs were prevalent across cancer types, genes, and patient age. Importantly, 8.1% of PGVs (50) were not reported by tumor sequencing as either somatic or germline findings. Among patients with PGVs, 11.2% (69) had their PGVs identified only after presenting with a second, possibly preventable, primary malignancy. Variants were often observed in patients with cancers not strongly associated with their germline findings, such as lung cancer and CNS tumors. *Conclusions:* As a follow-up to tumor sequencing, germline tests can inform clinical management decisions. Current guidelines and tumor testing approaches capture many, but not all, of these germline findings, reinforcing the utility of both expanded germline reflex testing, as well as germline analysis independent of tumor sequencing in appropriate patients.

### Carriers' Experience and Attitudes Towards the Australian Jewish Brca2/2 Community Screening Program

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*Background:* Individuals of Jewish Ancestry have approximately a 1 in 40 chance of testing positive for three Jewish Founder Mutations in *BRCA2* and *BRCA1*. An Australian first Jewish *BRCA2/2* screening program (JeneScreen) was offered in two Australian metropolitan cities. The cities used different pretest information delivery and consent methods; one via a website (online) and the other via community seminars (community). This substudy aimed to explore the experiences of participants who tested positive through JeneScreen. *Methods:* *BRCA2/2* positive JeneScreen participants were invited to partake in the substudy via email. Semistructured telephone interviews were conducted to explore experiences of the pretest method, receiving results, and participating in the program. Interviews were analyzed using an inductive thematic analysis. High coding concordance was achieved across three coders. *Results:* Three online and nine community participants were interviewed, 11/12 were analyzed, identifying three key themes: (1) Appreciation of JeneScreen reflects participant's feelings about the screening program. (2) Feeling supported relates to the participants' experiences throughout the JeneScreen genetic testing experience. (3) 'JeneScreen, it is an easy process' encompasses the participants' perceived benefits of population screening and the use of streamlined methods. All participants were supportive of a *BRCA2/2* screening program and most preferred the pre-test method they received. *Conclusion:* Both online and community participants expressed high satisfaction with the screening program. This study suggests that a website and community seminars are suitable replacements for face-to-face pre-test counseling in a *BRCA2/2* Jewish founder mutation screening program.

### A Germline Novel Truncating MECOM Variant in a Patient with a Family History of Thrombocytopenia

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*Background:* Pathogenic variants in the *MECOM* gene are associated with amegakaryocytic thrombocytopenia with/without radioulnar synostosis (OMIM:616738). *Aim:* Most cases reported to date have required transplants at relatively young ages. We present a family with mild thrombocytopenia without radioulnar synostosis with a likely pathogenic variant detected in the *MECOM* gene, who have not required a transplant. *Case Description:* A 54-year-old male, diagnosed at birth with thrombocytopenia, with spontaneous

improvement at 12 months of age. At age 11, he was again diagnosed with aplastic anemia that has persisted. His father had thrombocytopenia, a sister diagnosed at age 59 with mild intermittent thrombocytopenia and neutropenia, a brother who died aged 8 years with aplastic anemia and a brother who was stillborn. *Method and Results:* Next-generation sequencing was performed on the proband's germline (hair) DNA sample and his sister's blood-derived DNA sample with analysis restricted to genes within a comprehensive bone marrow failure panel. Analysis detected a likely pathogenic truncating mutation in the *MECOM* gene (NM\_004991.3): c.816dupT resulting in p.(Pro273Serfs\*2). *Conclusion:* This early-truncating *MECOM* mutation, located in the first zinc finger, is likely a complete loss of functional allele. *MECOM* mutations that cause thrombocytopenia and bone marrow failure with radioulnar synostosis described to date are missense mutations in the second c-terminal zinc finger. Stillbirth seems to be a feature of *MECOM* with postmortem analysis of several fetuses in affected families showing hypocellular BM. As well as stillbirth, this family is among the mildest and oldest mutant *MECOM* patients described to date.

### Clonal Hematopoiesis as a Natural Functional Assay of *TP53* Germline Variant Pathogenicity: Updated Results From Two Laboratories

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Approximately 30% of *TP53* variants identified in the blood of patients undergoing genetic testing for hereditary cancer are suspected to have somatic origin, mostly due to clonal hematopoiesis (CH), and this proportion increases with lower variant allele fraction (VAF). Positive selection has been proposed to be a mechanism driving CH, with somatic variants providing fitness advantage to a subset of blood cells. For this reason, we hypothesized that *TP53* variants with low VAF are pathogenic drivers of CH. If true, low VAF status could be used a positive predictor of *TP53* variant pathogenicity. We used VAF data from 1100 pathogenic variants and 65291 benign variants from Ambry Genetics, in addition to 355 pathogenic variants from Peter MacCallum Cancer Centre. Variants present in the homozygous state or in individuals affected with a hematological malignancy had been excluded. VAF distribution was strikingly different between the groups: benign variants showed an expected normal distribution around 50:50 ratio, while pathogenic variants showed a bimodal distribution. We compared the proportion of pathogenic and benign variants observed in different VAF bins, and determined that VAF <30% provided strong evidence towards pathogenicity (likelihood ratio >100). We found that this evidence type could be applied to ~25% of *TP53* germline variants of uncertain significance. This data confirms that CH is a distinctive characteristic of pathogenic *TP53* variants, and provides a new interpretation of this phenomenon. It can be used as a natural functional assay to assist with the interpretation of *TP53* germline variants.

### The Impact of Variants at Branchpoint Splicing Elements in Cancer Genes

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*Background:* Branchpoint elements are required for intron removal, and variations in these elements can result in aberrant splicing. *Aim:* We aimed to assess the value of branchpoint annotations generated from recent large-scale studies to select branchpoint-abrogating variants, using hereditary cancer genes as model. *Methods:* We identified branchpoint elements in 119 genes associated with hereditary cancer from three genomewide experimentally inferred and two predicted branchpoint datasets. We then identified variants from public databases that occur within branchpoint elements. We compared conservation, unique variant observations, and population frequencies at different nucleotides within branchpoint motifs. Finally, selected minigene assays were performed to assess the functional impact of variants in branchpoint elements within mismatch repair genes. *Results:* We annotated 4,973 branchpoints (3,012 experimentally inferred) in hereditary cancer genes. There was poor overlap between predicted and experimentally inferred branchpoints. We found 6,494 single nucleotide variants were located in experimentally inferred or predicted branchpoint motifs. Our analysis of cancer genes suggested that variants at -2nt, -1nt, and branchpoint positions in experimentally inferred canonical motifs are more likely to be clinically relevant. Minigene assay data showed the -2nt to be more important to branchpoint motif integrity, but also demonstrated fluidity in branchpoint usage. *Conclusion:* Data from cancer gene analysis suggests that there will be few high-risk alleles that severely impact function via branchpoint abrogation. Results inform a general scheme to prioritize branchpoint motif variants for further study.

### Exploring the Implementation of Comprehensive Genomic Breast Cancer Risk Assessments

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*Background:* Genomic risk assessments (GRAs) can stratify women's risk of developing breast cancer (BC), into clinically actionable risk categories. Women's attitudes on GRAs must be understood to inform implementation in a person-centered manner to promote population acceptance and participation. *Aim:* To explore women's attitudes of GRAs and determine what test-specific and test-delivery

factors would influence their decision to participate. *Methods:* 31 women with no personal history of breast cancer, with and without a family history of BC, participated in focus group discussions or personal interviews. Participants were explained the concept of BC-GRAs before discussing their perceptions of the test. Qualitative analysis was undertaken through inductive coding. *Results:* Participants responded positively. Identified themes include that acceptance hinges on the actionability of results, as women value the ability to inform decision-making and access risk-appropriate screening. Participants report they may be deterred by anxiety, stress, or the potential for genetic discrimination. Participants also highlighted the importance of the age GRAs are offered, how accessible they are, and how results are returned. *Discussion:* Women acknowledged effective implementation of GRAs relies on their ability to inform BC-risk mitigation. While women with a strong family history value the opportunity for GRAs to inform increased breast surveillance, women with low-risk results may feel discomfort accepting reduced breast surveillance as they find reassurance in regular screening. Meanwhile, women with no breast cancer family history may lack the stimulus to undertake genomic testing, which highlights the need for population education on the importance of engaging in GRAs and BC-risk mitigation.

### miRNA Regulation of Moesin in Lymphoma: A Deadly Relationship?

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Non-Hodgkin's lymphoma (NHL) subtypes can be difficult to treat, even with an array of therapeutic agents on hand. Studies have highlighted Moesin (*MSN*) to be a potential marker of aggressive lymphoid malignancies such as Burkitt's lymphoma and DLBCL, and therefore a potential therapeutic target. To pave the way for improved targeted interventions, further understanding of the exact drivers behind *MSN*-initiated lymphomagenesis is required. To date, there is no clear literature on the relationship between miRNA:*MSN* regulation and NHL development and progression, therefore this project aims to undertake focused epigenetic and functional studies on *MSN* across various tissues to uncover its role in lymphomagenesis. Results to date have shown that specific miRNAs of interest regulate pathways, such as Janus kinases - signal transducer and activator of transcription proteins and signal transducer and activator of transcription proteins (*STAT4*), as well the regulation of critical cellular functions such as proliferation, formation of cytoskeleton, and cytokine signaling. *MSN* expression in NHL was upregulated in Burkitt's lymphoma and diffuse large B-cell lymphoma cell lines, suggesting *MSN* may prove to be a novel biomarker for risk and disease progression in specific NHL subtypes. Further investigations into miRNA:*MSN* targeting across NHL patient peripheral blood and tumor samples will enable a clearer understanding of *MSN*'s involvement in critical pathways which are associated with NHL.

### 'My New Normal': Experiences of Prophylactic Gastrectomy for Young Adults with a *CDH1* Pathogenic Variant

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*Background:* Unaffected individuals with a *CDH1* pathogenic variant are recommended to have prophylactic total gastrectomy (PTG) from age 20 to 30 years to manage their significantly increased lifetime risk for diffuse gastric cancer. Despite the recommended timing of PTG, there is limited evidence of the impact of this major surgery on young adults; a distinct cohort with unique developmental considerations. *Aim:* This study aimed to explore the impact and experiences of PTG for young adults. *Methods:* Young adults aged 18–39 years with a *CDH1* pathogenic variant were invited from the Parkville Familial Cancer Centre to participate in a semistructured telephone interview. Interviews were audio-recorded, transcribed, and deidentified. Team-based thematic analysis was undertaken using an iterative and inductive process over several coding rounds. *Results:* Thirteen participants participated in interviews, nine of whom had proceeded with PTG. Participants reported a range of short- and long-term physical and psychosocial sequelae, experiencing more negative than positive impacts on their body image and recurrent hospitalizations. Most participants discussed extensive changes to their relationship with food and explored different adaptive strategies, including step-by-step and trial-and-error eating and altered social practices. Positive impacts of PTG included an increased sense of empowerment and control over cancer risk and stronger connections with social supports. *Conclusion:* This is the first study of its kind in Australia. These findings inform genetic counseling and gastroenterology practice by highlighting the need for holistic discussions of the possible impacts of PTG pre-surgery and the necessity of longer-term support as young adults navigate their new normal.

### Modeling Pathogenic Germline Variants to Understand Inherited Bone Marrow Failure and Predisposition to Myeloid Malignancy

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*Background:* Through the Australian Familial Hematological Cancer Study (AFHCS), we have identified causal germline variants in



several inherited bone marrow failure disorders. We identified that heterozygous germline mutations in *GATA2* underlie an array of complex hematopoietic and lymphatic diseases with a predisposition to leukemia. *Aim and Methods:* To define mechanisms by which pathogenic *GATA2* variants cause disease, we have generated a mouse model representing the most common germline *GATA2* (T354M) variant and characterized associated phenotypes. *Results:* Homozygous loss of *GATA2* results in embryonic lethality between E10-10.5 in mice. Interestingly, in contrast to this, we have successfully generated *Gata2*<sup>T354M</sup> homozygous mice though they are born at a less-than-expected ratio. Consistent with previous in vitro findings, this indicates that the T354M variant is not a complete loss-of-function mutation. Peripheral blood and bone marrow analysis shows a marked reduction in lymphocytes and monocytes in *Gata2*<sup>T354M</sup> homozygous reflecting the immunodeficiency observed in patients. Furthermore, colony assays show a marked bias towards the granulocytic lineage and reduced macrophage differentiation. This model has also uncovered other potential underlying nonhematopoietic features such as osteopenia and urogenital abnormalities which are likely missed or underreported in patients. We are further investigating these mice, with particular emphasis on response to hematopoietic stressors and modeling autologous gene-edited stem cell transplantation, to better understand mechanisms of disease onset and prevent progression. *Conclusion:* Approaches to evaluate novel germline variants and uncover biological pathways affected in known germline pathogenic variants will provide insight facilitating advancements in diagnosis, personalized treatment, and possibly even prevention strategies.

### A Pilot Study Investigating the Health Economics of Achondroplasia in Australian Children

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*Background:* There are no approved therapies for achondroplasia that address the underlying pathophysiology. Vosoritide, a C-type natriuretic peptide analogue, has been developed by BioMarin Pharmaceutical and has demonstrated increased growth velocity in children with achondroplasia. If Therapeutic Goods Administration approval is granted for this potentially expensive medication, economic justification might assist in a Pharmaceutical Benefits Scheme listing/orphan drug designation, enabling all eligible Australian children to access this precision medication. *Aim:* To conduct a pilot study to better understand the economic impact of achondroplasia on the Australian healthcare system in children aged 0–5 years. *Methods:* Using standard of care information from The Royal Children's Hospital Melbourne and incidence/prevalence of complications, a cost analysis was performed to determine the approximate medical costs in this cohort. *Results:* A child with achondroplasia receiving standard care may cost the healthcare system between \$27,787 and \$160,273 by age 5 years, depending on the presence of associated medical complications such as hearing loss, otitis media, cervicomedullary compression, hydrocephalus and sleep apnea. *Conclusions:* These results demonstrate that the medical costs of children with achondroplasia are significant. Further investigation into other costs across the lifespan of this condition is required. The impacts this treatment may have on each individual, regardless of economic cost, must also be considered, as

improvement in medical, functional, and psychosocial wellbeing have significant impacts on quality of life.

### Voretigene Neparvovec in Patients With *RPE65* Mutation Associated Inherited Retinal Dystrophy: Baseline Characteristics From the Real-World, Prospective, Observational Perceive Study

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*Background:* Voretigene neparvovec (VN) is the first approved ocular gene therapy for treating patients with confirmed biallelic *RPE65* mutation-associated inherited retinal dystrophy. PERCEIVE, a registry-based post-authorization safety study designed to assess long-term safety of VN in a real-world (RW) setting. Here, baseline characteristics of participating patients treated with VN are reported. *Aim:* The objective of the study is to characterize the long-term safety profile of VN, to follow pregnancy outcomes, and to assess visual function over time. *Methods:* PERCEIVE is an ongoing, prospective, longitudinal, multicenter observational, safety study. All VN-treated patients are encouraged to participate in the study. After receiving VN, patients are followed-up as per the routine medical care for 5 years. *Results:* At data cut-off, of the 15 patients enrolled, 10 patients (16 eyes) have received VN. At the time of enrollment, the mean (standard deviation [SD]) age was 27.6 (9.81) years with a range of 15–51 years (1 adolescent; 9 adults). For the treated eyes ( $n = 16$ ), baseline mean (SD) visual acuity was 0.96 (0.37) logMAR ( $n = 14$ ; range: 0.5–1.6 logMAR), and full-field stimulus threshold (white light) was  $-4.32$  (9.40) dB ( $n = 15$ ; range:  $-34.9$  to 3.2 dB). Optical coherence tomography (OCT) revealed a mean foveal thickness of 150.5 (41.07)  $\mu\text{m}$  ( $n = 15$ ; range: 76–216  $\mu\text{m}$ ). Central OCT showed that 11 eyes had an outer nuclear layer with a thickness range of 36–74  $\mu\text{m}$  ( $n = 9$ ), while it was absent in 4 eyes. The ellipsoid zone line was disrupted in nine eyes and was undetected in six. *Conclusions:* PERCEIVE provides valuable information on baseline characteristics of this vision-impaired population, and effect of VN therapy in a RW setting.

### Implementation of a Dedicated Ocular Genetics Clinic: Integrating Genetic Testing and Counseling into Ophthalmic Care

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Historically, genetic testing for patients with inherited eye disease typically occurred through clinical genetics services based on non-specialist hospitals or via research programs. With ophthalmology

being at the forefront of gene therapy and treatment strategies, timely genetic testing is important in the delivery of expert care for these families. The Royal Melbourne Hospital (RMH) clinical genetics service and the Royal Victorian Eye and Ear Hospital (RVEEH) have initiated a combined multidisciplinary Ocular Genetics Clinic (OGC) based at the RVEEH to address this need. The service is comprised of ophthalmologists, orthoptists, clinical geneticist, and genetic counselors. A retrospective audit of the families seen in OGC covering the period between December 2018 and April 2021 was conducted by reviewing the medical records, with a focus on genetic testing and outcomes. In this period, 378 patients have attended OGC with a total of 259 genetic tests ordered, including diagnostic, predictive, confirmatory, and segregation testing. Of these, 116 diagnostic results have been received and disclosed to patients. The diagnostic rate during this time was 65%, with pathogenic or likely pathogenic variants detected in 75 patients, confirming their clinical diagnosis. Eleven patients had variants of uncertain significance identified and are currently undergoing segregation. Of the remaining cases, a molecular diagnosis was not made in 30 patients. The implementation of the OGC is achieving its aims of providing expert care to families through increased access to genetic testing and identifying accurate diagnoses. This is critical in a field where treatment strategies are evolving rapidly.

### Active and Passive Implementation of Recommendations for Management of Rare Diseases: A Systematic Review

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**Background:** Delivering evidence-based care to people with rare conditions is difficult. There is often scant high-quality evidence, health professionals may not have seen a presentation before, and conditions may be 'invisible' in the system. However, the recent rise of rare disease networks and international genomic alliances is contributing to a growing body of recommendations for rare diseases. **Aim:** To systematically review the peer-reviewed literature and to examine how recommendations were being implemented for the management of rare conditions. **Methods:** We searched Medline, EMBASE, Web of Science, and CINAHL using search strings for rare diseases AND practice guidelines, AND implementation/real-world use, with no date limits. **Results:** We found 495 articles with 103 undergoing full-text review. Only one article fully met our criteria of implementation of rare disease recommendations. This was a project across a region's emergency departments to optimize testing equipment, processes and staff knowledge for a time critical acute presentation of a rare disease. Most of the 103 papers described the development of consensus-based recommendations, reflecting the scarcity of evidence. The audience for the recommendations was often vaguely described and lacked specific information on who should do what. Many papers relied on passive dissemination by publication in a specialist journal, or flagged the inclusion of the guidelines in a rare disease repository. **Discussion:** Developers of consensus-based recommendations should be clear on the intended audience and have clear robust processes and an implementation plan/directions on how to operationalize the recommendations.

### Diagnosis of Low-Level Constitutional Mosaic Trisomy 12 by High-Resolution Microarray

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**Background/Aim:** High-resolution microarray (HRM) provides more sensitive detection of constitutional chromosomal anomalies than single nucleotide polymorphism (SNP) array [Illumina Infinium GSA-24 v 2.0]. **Methods:** We first investigated an infant with atrial septal defect (ASD), right ventricular dysfunction, hypotonia, visual impairment, and dysmorphic features including blepharophimosis, posteriorly rotated low-set ears and anterior anus with SNP array and singleton exome sequencing (ES) performed on DNA extracted from saliva, which was uninformative. Subsequent HRM analysis [Illumina Infinium GDA-8 v1.0] was performed on DNA extracted from saliva. Fluorescence in-situ hybridization (FISH) on paraffin-embedded cardiac tissue was used as orthogonal confirmation of the HRM analysis. **Results:** HRM identified mosaic trisomy 12 in approximately 5% of cells in the saliva sample. The patient had undergone ASD repair with biopsy demonstrating interstitial fibrosis and endocardial fibroelastosis. FISH analysis of cardiac tissue confirmed mosaic trisomy 12 in 5% of cells (10 out of 200 cells analyzed). **Discussion:** HRM allowed for the detection of 5% trisomy 12 mosaicism in our patient, with the same finding validated using FISH on cardiac tissue. Mosaic trisomy 12 is a rare postnatal diagnosis. Affected individuals have a variable presentation most consistently characterized by facial dysmorphism, congenital heart disease, and hypotonia. The phenotype of our patient is consistent with that of other published cases of mosaic trisomy 12 in the literature. HRM should be considered for the detection of causative low-level mosaic chromosomal aneuploidies in those who remain undiagnosed after clinical exome and standard microarray.

### Delineation of the Clinical and Molecular Spectrum of *QRICH1* Associated Neurodevelopmental Disorder

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**Background/Aim:** De novo *QRICH1* variants have been reported in 11 individuals with developmental delay, autism spectrum disorder, short stature, facial dysmorphism, and chondrodysplasia. We present 27 additional individuals to further delineate the phenotypic and genotypic spectrum of this emerging neurodevelopmental disorder. **Methods:** Phenotypic and molecular data were gathered through international collaboration and compared to those of the previously reported individuals. **Results:** Frequent phenotypic features included mild to moderate developmental delay/intellectual disability (71%),

nonspecific facial dysmorphism (92%), and hypotonia (39%). Additional findings were poor weight gain (29%), short stature (29%), autism spectrum disorder (29%), seizures (24%), and scoliosis (18%). Minor structural brain abnormalities were reported in 52% of the individuals with brain imaging. Truncating or splice variants were found in 28 individuals and 10 had missense variants. Four variants were inherited from mildly affected parents. **Conclusion:** This study confirms that heterozygous *QRICH1* variants cause a neurodevelopmental disorder and short stature and expands the phenotypic spectrum to include poor weight gain, scoliosis, hypotonia, minor structural brain anomalies, and seizures. Inherited variants from mildly affected parents are reported for the first time, suggesting variable expressivity. Conclusions regarding phenotypic differences between individuals with missense variants as compared to loss-of-function variants are limited by sample size.

### Brain Malformation and White Matter Abnormalities Associated With LSS-Related Neuroectodermal Syndrome

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**Background:** Disorders of cholesterol biosynthesis encompass a broad range of phenotypes with overlapping features, including intellectual disability, brain and limb malformations, and ectodermal defects. Bi-allelic mutations in *LSS*, encoding lanosterol synthase, recently were found to cause a spectrum of abnormalities beyond cataract, including hypotrichosis and a severe neuroectodermal syndrome (MIM#618840) with some genotype-phenotype correlation. This phenotype has been recapitulated in a murine model with lanosterol synthase deficiency in affected tissue. **Aim:** To describe the neuroimaging abnormalities in patients with the *LSS*-associated alopecia and intellectual disability syndrome. **Methods:** Individuals with bi-allelic mutations in *LSS* and abnormal CNS neuroimaging were identified via international neurogenetic research collaborations. Previous reports of *LSS*-associated alopecia and intellectual disability syndrome were reviewed for neuroimaging abnormalities. **Results:** Four unrelated individuals were identified. CNS abnormalities in these individuals and previous reports include holoprosencephaly, cortical malformations, periventricular nodular heterotopia, cerebral atrophy, open opercula, cerebellar dysplasia, abnormal myelination, and corpus callosum dysgenesis. All four patients had congenital alopecia and epilepsy, and additional malformations included cleft palate, polydactyly, and genital hypoplasia. Sterol analysis identified an increased level of desmosterol in one individual, consistent with *in vitro* studies that show inhibition of desmosterol reductase by oxidosqualene as a feature of partial deficiency of *LSS*. **Conclusion:**



LSS-associated neuroectodermal syndrome causes a spectrum of clinical features characterized by hypotrichosis and intellectual disability with or without epilepsy, brain malformation, and white matter abnormality. The cholesterol metabolism pathway is a potential target to modify the developmental and epileptic phenotype and warrants further investigation.

### Incorporating the Patient Perspective: Systematic Review of Outcomes in Qualitative Studies Evaluating the Patient Experience of Reproductive Genetic Carrier Screening

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**Background:** The Core Outcome Development for Carrier Screening (CODECS) study aims to develop a consensus-derived set of outcomes to measure in studies of reproductive genetic carrier screening (RGCS). This multistep process first involves reviewing published research literature to capture outcomes reported to date. In a previous systematic review of outcomes in quantitative studies offering RGCS, few studies included patient-reported outcomes. As a result, the patient perspective was lacking. **Aim:** To conduct a systematic review of qualitative studies reporting on the patient experience of RGCS, with the objective to identify outcomes of importance to patients. **Methods:** Medline, EMBASE, PsycINFO, and CINAHL were searched for published studies offering RGCS. Text excerpts capturing quotations and themes were extracted verbatim and a deductive analysis was conducted to code excerpts as research outcomes. **Results:** Sixteen studies from 2010 to 2020 were included. We identified 73 outcomes, belonging to 15 outcome domains. Most outcomes were consistent with those identified in the previous review of quantitative studies; however, reproductive confidence and empowerment were identified as an outcome unique to the qualitative literature. **Conclusion:** This is the first example of a qualitative approach for determining outcomes of importance to patients undergoing RGCS. The patient concept of personal utility, defined by reproductive confidence/empowerment, is absent from existing quantitative studies and suggests a novel dimension for future research to address. A core objective of the CODECS study is to involve patients in defining outcomes of importance for future research, which will enhance the relevance of research findings and maximize translation into patient-centred clinical practice.

### Intragenic de Novo Deletions In *TAOK1* Resulting in Severe Neurodevelopmental Disorder

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**Background:** Single nucleotide variants in *TAOK1* have recently been associated with a neurodevelopmental disorder characterized by intellectual disability, hypotonia, joint hypermobility, and early feeding difficulties. A range of molecular mechanisms has been proposed, including loss of function and dominant negative effects. **Methods:** Copy number variant analysis was performed on exome data from a child with profound neurodevelopmental disability. Additional cases were sought in an internal laboratory database. Findings were

validated on a high-resolution SNP microarray platform. **Results:** A de novo intragenic deletion of exons 3–11 of *TAOK1* was detected and confirmed on microarray. A second individual with a de novo deletion of exons 2–10 was identified. Both deletions result in the complete loss of the *TAOK1* kinase domain. The affected individuals previously had uninformative clinical exome and microarray testing and have a strikingly similar phenotype comprising profound intellectual disability, microcephaly, and seizures, with a clinical diagnosis of cerebral palsy. Brain MRI demonstrated marked ventricular dilatation and decreased white matter in both children, with progressive cerebral and cerebellar atrophy on serial imaging in one. **Discussion:** Our findings suggest that intragenic deletions affecting the N-terminal region kinase domain of *TAOK1* result in a particularly severe phenotype. We highlight the importance of incorporating CNV analysis of exome data as part of the routine diagnostic practice. Small recurrent intragenic deletions in *TAOK1* may be an under-recognized causative explanation for patients with similarly severe neurodevelopmental phenotypes.

### Childhood Prevalence of Achondroplasia in New South Wales (NSW) and the Australian Capital Territory (ACT), Australia

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The aim of this study was to estimate the childhood prevalence of achondroplasia, trends over time in birth prevalence, and age at diagnosis in Australia. Children born between 1990 and 2019 with a clinical and radiological and/or molecular diagnosis of achondroplasia were identified from a tertiary hospital servicing New South Wales (NSW) and the Australian Capital Territory (ACT) and compared with population data from the Australian Bureau of Statistics. Childhood prevalence of achondroplasia, based on children  $\leq 19$  years of age and resident in NSW/ACT on June 30, 2019 ( $n = 109$ ), was 5.2 per 100,000. A total of 127 individuals with achondroplasia were born in 1990–2019 in NSW/ACT. Birth prevalence rates increased across birth decades, from 3.3 per 100,000 live births in 1990–1999 to 5.3 per 100,000 in 2010–2019 ( $p < .0001$ ). Median age at diagnosis decreased to 17 days in 2010–2019 compared with 30 days in 1990–1999 ( $p = .035$ ), although the overall decreasing trend across consecutive decades did not reach statistical significance. This is the first study to show a rising birth prevalence rate for achondroplasia in Australia with a concurrent decreasing age at diagnosis, both of which were statistically significant after two decades.

### Mitochondrial Disease Diagnosis Via Next Generation Sequencing

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**Background:** Mitochondrial diseases represent a group of metabolic and neurological disorders characterized by defects in mitochondrial energy generation caused by mutations in mitochondrial DNA



(single nucleotide variants (SNV) and larger deletions) and/or the nuclear genes encoding mitochondria. In 2019, VCGS introduced a new high coverage next generation sequencing (NGS) assay which simultaneously detects both (SNV) and large deletions in the mitochondrial genome, aiming to consolidate testing and increase diagnostic yield. *Method:* An audit of clinical data from the first 2 years of the NGS assay was undertaken to ascertain whether an increase in diagnostic yield could be achieved compared with a long-standing targeted assay containing a limited number of 22 common mitochondrial DNA mutations. *Results:* Data from 113 patients from across Australia was reviewed. Diagnostic results were issued for 34 patients (26 SNVs and 8 deletions). Potentially diagnostic variants of uncertain significance (Class 3a) were identified in a further 10 patients and 69 negative results were reported. The overall diagnostic rate was 30%. One patient was diagnosed with multiple deletions indicating a possible nuclear gene mutation and the need for subsequent exome or whole genome sequencing (WGS). Compared with the original targeted 22 variant panel, 18 additional diagnoses (8 deletions and 10 SNVs) were reported via the NGS assay, representing a doubling of diagnostic yield. *Conclusion:* Improved outcomes for patients can be achieved with increased diagnosis of mitochondrial disease by embracing rapidly advancing genomic technology, including whole mitochondrial genome analysis coupled with exome, or as part of WGS.

### Implementing a Patient-Centered Care Model to Diagnose Maturity Onset Diabetes of the Young (MODY)

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*Background:* MODY is the most common monogenetic form of diabetes and often misdiagnosed as type 1 or type 2 diabetes. Currently, genetic testing is usually undertaken by genetics professionals following referrals to a genetics clinic. The implementation of a patient-centred model of care will allow nongenetics professionals to arrange MODY testing during routine clinical care. This care model is hypothesized to improve treatment experience and outcomes for patients. *Aim:* Implement a model of care for MODY genetic diagnosis; assess the comfort levels and support needs of Endocrinologists and psychosocial stress for patients; develop clinical guidelines and criteria for MODY testing. *Methods:* Eligible patients attending Diabetes Clinic are invited to participate by the treating endocrinologist. MODY testing is arranged following consent by endocrinologists at point-of-care. Results are returned by endocrinologists and used to guide patient management. Data are collected via patient demographic clinical data form at enrolment, modified Genetic Counseling Outcome Scale at pre- and post-testing, clinician experience questionnaire at the end of study. Analysis includes comparisons between pre-test and post-test scores and percentages used to summarize categorical data. *Results:* To date, 41 patients have been recruited by 15 endocrinologists. Of the patients who have received genetic testing results, a MODY diagnosis was achieved in 19% (4/21). Preliminary data showed all patients consider point-of-care MODY testing beneficial. There was an increase from 46% at pretest to 89% at posttest in patient's knowledge and confidence in sharing MODY information with their

relatives. *Conclusion:* Mainstreaming MODY testing is feasible and beneficial for patients.

### A De Novo Missense Variant in MED13 in a Patient With Global Developmental Delay, Marked Facial Dysmorphism, Macroglossia, Short Stature, and Macrocephaly

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*Background:* Variants in Mediator complex subunit 13 (*MED13*, OMIM 603808) have been reported in individuals with mild-moderate intellectual disability (ID) and/or developmental delay (DD). *Aim:* To expand the phenotypic spectrum of the *MED13*-associated syndrome by describing an additional individual found to have a de novo heterozygous missense variant in *MED13* with more pronounced features than in the 20 individuals previously identified. *Case Description:* The proband was born at term following an unremarkable antenatal course. Early developmental milestones were significantly delayed. Sitting and walking did not occur until 3 and 4.5 years, respectively. The individual was nonverbal at 5 years of age, displayed autistic behaviors, and suffered from constipation. At 6 years of age, he was short (1st centile) and macrocephalic (99th centile). Marked dysmorphism was observed, including macroglossia, small midface, and down-slanting palpebral fissures. *Results:* A trio clinical exome analysis identified a likely pathogenic class IV de novo variant in the *MED13* gene NM\_005121.2:c.3449G>A (p.Gly1150Glu). *MED13* comprises part of a four-subunit kinase module regulator (the 'Module') of Mediator. Mediator is a large multiprotein complex which promotes the transcription of protein-coding genes by RNA Polymerase II. The Module-Mediator complex, facilitated by *MED13*, is postulated to both promote and inhibit transcription. It follows that *MED13* is a compelling candidate gene pertaining to neurodevelopmental disability. *Conclusion:* The neurodevelopmental profile of the proband is consistent with other described individuals, who were reported to have autistic features, speech delay, and constipation. However, this presentation was markedly more severe, expanding the phenotypic spectrum of *MED13*-associated syndrome.

### Qualitative Exploration of Patient and Caregiver Experiences of Visual Function Impairments and Impacts on Vision-Dependent Activities of Daily Living and Health-Related Quality of Life Associated With Retinitis Pigmentosa and Leber Congenital Amaurosis in Germany and France

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*Background:* Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) are rare inherited retinal degenerative disorders (IRD). Visual impairments associated with these disorders have significant

impacts on patients' vision-dependent activities of daily living (ADL) and broader health-related quality of life (HRQoL). There is a paucity of evidence exploring the patient experience of RP/LCA and how these impairments impact patients' lives across different genotypes. *Aim:* This study aimed to explore the experience of RP/LCA from patient and caregiver perspectives, across different genotypes and ages in Germany and France. *Methods:* Thirty semistructured qualitative concept elicitation interviews were conducted with 9 adults, 5 adolescents, 5 children, and 11 caregivers of children aged 3–11 years. The sample included different gene mutations linked to RP/LCA: *RPE65* ( $n = 11$ ), *RPGR* ( $n = 5$ ), *CEP290* ( $n = 3$ ), *AIPL1* ( $n = 2$ ), *LRAT*, *PDE6B*, *RDH12*, and *RP2* ( $n = 1$  each). Thematic analysis of verbatim interview transcripts was performed. *Results:* Night blindness, peripheral vision, and contrast sensitivity limitations were the most frequently reported visual function symptoms. Severity of impairments depended on lighting conditions and familiarity of the environment. Proximal vision-dependent impacts included limitations to mobility and ADLs. Participants reported impacts on broader HRQoL domains like emotional wellbeing, social, and work/school functioning. Similar concepts were reported by caregivers. *Conclusions:* Visual function symptoms and impacts on vision-dependent ADLs and HRQoL were consistent across age groups and genotypes, suggesting the same measures may be appropriate for use in all RP/LCA types. Findings increased the understanding of the qualitative experience of RP/LCA and supported the development of fit-for-purpose patient- and observer-reported outcome measures for use in RP/LCA clinical trials.

### An Australian Monogenic Inflammatory Bowel Disease Cohort: Literature Review and Study Design

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*Background:* Inflammatory bowel disease (IBD) is a multifactorial disease resulting in chronic intestinal inflammation. The genetics of IBD is complex and mostly polygenic. Advances in NGS however, have revealed monogenic etiologies in a subset of patients. Monogenic IBD is rare, severe, and refractory to conventional therapies; however, descriptions of gene-specific treatment strategies are emerging. *Aim(s):* (1) Understand the age distribution, clinical phenotype, and targeted therapies in monogenic IBD. (2) Curate a current IBD gene list. (3) Recruit an Australian cohort of potentially monogenic-IBD patients. (4) Apply genomic sequencing to study monogenic-IBD within this cohort. *Methods:* A literature review, addressing aim (1), was conducted and selection criteria identifying patients with likely monogenic-IBD were formulated. A clinically valid gene list was curated utilizing PanelApp and ClinGen guidelines. Patient recruitment has commenced through SCH. *Results:* The literature revealed more than 75 monogenic-IBD genes. Clinical features suggestive of monogenic-IBD include age of onset (<2 years), family history, perianal disease, treatment failure, recurrent infections, and extraintestinal manifestations. Most monogenic-IBD is refractory to standard therapies. HSCT improved IBD in patients with some monogenic forms of IBD but had poor outcomes in others. The curated gene list has been implemented locally (SEALSPathology) and nationally (PanelAppAustralia — ongoing) and genomic testing has begun. *Conclusion:* The literature review identified criteria for pediatric

IBD patient prioritization for genomic sequencing and commenced the creation of a curated IBD gene list. We will continue recruitment through SCH and potentially other sites, to study the distribution of monogenic-IBD and the impact of genomics on treatment modalities.

### Qualitative Interviews With Patients and Caregivers Regarding Visual Function Impairments and Impacts on Vision-Dependent Activities of Daily Living and Health-Related Quality of Life in RPE65-Related Retinitis Pigmentosa and Leber Congenital Amaurosis

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*Background:* Inherited retinal degenerative disorders (IRD) such as Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA) can be caused by mutations in the *RPE65* gene. These mutations cause visual function impairments which have significant impacts on patients' vision-dependent activities of daily living (ADL) and broader health-related quality of life (HRQoL). There is limited evidence on the patient experience of RP and no known genotype-specific experiences. *Aim:* This study aimed to explore the experience of *RPE65*-related RP/LCA from patient and caregiver perspectives. *Methods:* Semistructured qualitative concept elicitation interviews were conducted with 11 patients (7 adults, 1 adolescent, 3 children aged 6–11 years), and 5 caregivers of children aged 3–11 years. Patients had a clinical and genetic diagnosis of *RPE65*-related RP/LCA. Thematic analysis of verbatim interview transcripts was performed. *Results:* Night blindness, reduced peripheral vision, and problems with color vision were the most frequently reported visual function symptoms of *RPE65*-related RP/LCA. Proximal vision-dependent impacts included limitations to mobility and ADLs. Participants reported impacts on HRQoL domains including emotional wellbeing, social, financial, and work/school functioning. Severity of limitations varied based on lighting conditions and familiarity of the environment. Overall, similar concepts were reported across all participant groups. *Conclusions:* These findings provide in-depth insight into the visual function symptoms and impacts on vision-dependent ADLs and broader HRQoL associated with *RPE65*-related RP/LCA. Findings suggest that the visual function symptoms and impacts relevant to measure in clinical studies are consistent across RP/LCA genotypes. Interview findings contributed to the development of patient and observer-reported outcome measures specific to RP designed for use in clinical trials and to track disease severity in clinical practice.

### Cavitating Lung Lesions and Hemoptysis—A Rare Presenting Feature of Vascular Ehlers Danlos Syndrome

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*Background:* The vascular type of Ehlers-Danlos syndrome (EDS IV), caused by pathogenic variants in the *COL3A2* gene is the most

severe type of Ehlers-Danlos syndrome, often presenting with catastrophic arterial or organ rupture. Pulmonary manifestations including recurrent pneumothorax are a recognized feature. Recurrent life-threatening pulmonary hemorrhage is a rarely reported manifestation. *Aim:* To review the pulmonary manifestations of EDS IV by describing a family diagnosed with EDS IV following the death of a 17-year-old male who presented with recurrent hemoptysis. *Case Description:* The 17-year-old proband presented with an 18-month history of intermittent hemoptysis, vomiting, abdominal pain, and weight loss. CTPA demonstrated bilateral cavitating lung lesions of unclear etiology. He died suddenly after collapsing at home. The family were referred for genetic investigation when the proband's brother presented with omental infarction and incidentally detected similar cavitating pulmonary lesions. *Results:* Clinical exome analysis identified a variant of unknown significance in the *COL3A2* gene NM\_000090.3:c.1754G>T (p.585Val). Segregation testing demonstrated maternal inheritance. The proband's mother, who had a history of joint hypermobility, was subsequently found to have extensive arterial aneurysms consistent with EDS IV. The *COL3A2* variant segregated in a maternal uncle who also has features of a connective tissue disorder, and has been reclassified as likely pathogenic. *Conclusion:* Recurrent hemoptysis and cavitating lung lesions are a rarely reported manifestation of EDS IV, and should prompt consideration of an underlying connective tissue disorder. In this illustrative case, molecular diagnosis has enabled counseling and vascular surveillance for at-risk relatives.

### Outcomes of Genomic Sequencing for Families with Inherited Intellectual Disability — Where Next for Unresolved Families?

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*Background:* Inherited intellectual disability (ID) is highly heterogeneous, with over 700 monogenic causes. Genomic sequencing (exome/WES or genome/WGS) is the preferred platform for diagnostic approaches. *Aim:* To evaluate the diagnostic yield and clinical utility of genomic sequencing for families with two or more individuals with moderate-severe ID. *Methods:* Families known to the NSW GOLD service from 2008 to 2020 were assessed by the clinical team for suitability. Families were selected based on: (1) distinctive/severe phenotype (2) likelihood of resolving (3) clinical management (4) reproductive decision making. Whole genome sequencing was not available in Australia as an accredited diagnostic test at the time this project was conducted; therefore, sequencing was performed via Genome One or Australian Genome Research Facility with data analysis by the NSW Health Pathology Randwick Genomics laboratory. *Results:* Fifty-six families had genomic sequencing; 54 had WGS and two WES (one WES result pending). Twenty-one (38.2%) had

causative variants, two with novel genes identified. Three diagnoses impacted management. Several families required segregation and functional studies to validate variant pathogenicity. Families meeting all four criteria were more likely to have a diagnosis (44% diagnostic yield) compared to three (33%) or two (0%) criteria. WGS identified at least one pathogenic variant that would not be identified via WES. *Conclusion:* Genomic sequencing has high utility for resolving families with complex inherited ID. Outcomes of this study have influenced clinical directions for unresolved families who will have their data reanalyzed in 2–3 years, and enrolment in research-based analyses as part of our GOLD Unresolved ID Program.

### Investigating Healthcare Professional and Parent Acceptability of a System Using Face-Matching Technology for Individuals With Developmental Disorders

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*Background:* The FaceMatch project aims to use face-matching technology to increase the diagnostic rate and novel gene discovery for children with syndromic intellectual disability. *Aim:* This study aimed to assess the acceptance of FaceMatch by parents and healthcare providers. We investigated attitudes and understanding of FaceMatch, as well as the barriers and enablers to participation. *Methods:* Semistructured interviews were conducted with healthcare professionals ( $n = 10$ ) involved in diagnosing individuals with developmental disorders and parents ( $n = 7$ ) of children with developmental disorders. Healthcare professionals were recruited through professional networks of the team and snowball sampling. Parents were recruited through support groups. Interview data were analyzed using thematic analysis. *Results:* Attitudes towards FaceMatch were mostly positive. Enablers to engagement for both cohorts included altruism, information-seeking behaviours, and the potential benefit of FaceMatch as a diagnostic aid. Healthcare professionals reported that uptake was dependent on the effectiveness of FaceMatch in providing diagnoses. Some uncertainty existed around the relevance of the technology and its effectiveness in providing a diagnosis. Time and resources were identified as the primary barrier. Parent-reported barriers included some concerns about privacy and the emotional toll of searching for a diagnosis. *Conclusion:* Understanding healthcare professional and parent acceptability informed improvements to the FaceMatch platform. This included the development of clear communication about the project objectives, process, and result delivery. Such improvements will improve engagement and recruitment of participants into FaceMatch and should facilitate improved diagnostic rates for individuals with developmental disorders.

### A Retrospective Cohort Study of Medical Complications in an Australian Population of Children with Achondroplasia

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*Background and Objectives:* Achondroplasia is the most common skeletal dysplasia resulting in short stature in humans. Medical



complications of achondroplasia include craniofacial, ear, nose, and throat, orthopedic, respiratory complications, obesity, and death. This study aims to determine the rates of medical investigations, complications, and outcomes of interventions. *Methods:* Children and adolescents with Achondroplasia born between 2000 and 2019 with two or more episodes of care at our specialist clinic were included. Data were retrospectively collected from the clinical records on investigations, complications, interventions, and outcomes from 0 to 18 years of age. Standard descriptive statistics were used to analyze the frequency of these events and age of onset. *Results:* There were 108 participants, 58 males and 50 females. The mean length of follow-up was 9 years (SD 5.1 years) with median 29 (IQR32) outpatient and 2 (IQR5) inpatient attendances. Over 800 investigations were performed. There were 52 (48%) participants with craniocervical stenosis, 15 (13.9%) with hydrocephalus, 66 (61.1%) with hearing impairment, 44 (44.4%) with sleep disordered breathing, 46 (42.6%) with lower limb malalignment, 24 (22.2%) with thoracolumbar kyphosis, 10 (9.3%) with symptomatic spinal stenosis, 12 (11.1%) with obesity, and 16 (14.8%) who had at least one admission for respiratory illness. 2 (1.9%) children died during the study period. *Conclusions:* We report contemporary rates of medical complications in an Australian population of children with achondroplasia. This information will help guide clinicians with their expectant management of achondroplasia and provide context to families about the likelihood and timing of complications.

## CYTOGENETICS

### A Spreadsheet to Determine Clonal Proportions in a Broad Range of Situations

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*Background:* Cancerous tissues usually include some normal cells. B allele frequencies (BAF) in SNP arrays can be used to estimate the proportions of different clones in mosaic cell populations. However, aside from simple ratios such as 2:1, estimating these proportions from the BAF is not straightforward. *Aim:* To produce a spreadsheet for calculating the proportions of two clones that are mosaic for copy number gain or loss. *Methods:* Our method is based on Illumina SNP arrays. B allele frequency is (number of B alleles)/(total number of alleles). We reversed this formula to calculate the cell proportion when the copy number of the alleles in the two populations is known. We created a spreadsheet using this formula to determine clone proportions by inputting BAF and allele options. *Results:* The spreadsheet can be used to work out the proportions of two clones with known copy number differences. It also has wider applications: it can be used to work out the absolute proportion of A: B alleles, which would, for example allow the degree of amplification to be determined ( $nA:1B$ ). It can also be used where there is copy number neutral loss of heterozygosity (CN-LOH). It is therefore more versatile than tables that only cater for limited situations such as single copy loss or gain, or that are empirically derived. *Conclusion:* This spreadsheet is easy to use and can be used to determine the proportion of abnormal cells or the degree of amplification or CN-LOH.

### Two Unrelated Families with 5' Noncoding Duplications Upstream of MSX2 Refine the Critical Regulatory Region Likely Involved in Cranial Bone Development and a Cleidocranial Dysplasia-Like Phenotype

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*Background:* Intragenic *MSX2* variants result in distinct phenotypes including craniosynostosis and parietal foramina with or without cleidocranial dysplasia. We present two unrelated families with delayed closure of a wide anterior fontanelle and cranial sutures with inherited duplications upstream of *MSX2*. *Methods:* Genomic DNA was extracted from peripheral blood/saliva samples of the probands and their parents. Microarrays were performed using Illumina Infinium GSA-24 v2.0 (Family 1) and CoreExome-24 v1.1 (Family 2). *Results:* Patient 1 presented at 2 months with wide anterior fontanelle, clinodactyly, and normal clavicles. Microarray identified a 1.5 Mb duplication of chromosome 5q35.1q35.2 (hg19 chr5:172,412,553-173,888,281), 259kb upstream of *MSX2*. His mother had 40% mosaicism for the same duplication, but no skeletal or cranial abnormalities. Patient 2 presented at two months with wide anterior fontanelle and cranial sutures, but normal clavicles. Microarray identified a 600 kb duplication of chromosome 5q35.2 (chr5:173,416,324-174,025,065) 122 kb upstream of *MSX2*. Parental segregation identified maternal inheritance. Her mother in childhood had similar features with closure of her anterior fontanelle at 2.5 years. She is of normal adult height and cognition without dental anomalies. *Conclusions:* These duplications overlap with those previously reported in a 219 kb noncoding region upstream of *MSX2*, which contains several evolutionarily conserved noncoding elements that may act as specific enhancers of *MSX2*. These duplications are likely to alter the topological landscape around *MSX2*. Our observations strengthen the evidence for pathogenicity of copy number variations in this region and refine the critical region that may result in *MSX2* dysregulation and a cranial phenotype.

### Preliminary Study on the Cytogenomics of Uveal Melanoma

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Ocular melanoma, although rare, is the most common primary cancer of the eye in adults. 83% of tumors arise in the uvea (UM). First-line treatment options are resection, radiation therapy, and enucleation which provide good local disease control, but long-term survival is reduced by metastatic disease. UM exhibits recurring chromosomal abnormalities and gene mutations, which strongly correlate with tumor evolution and metastatic risk and because of this accurate cytogenomic profiling of UM tumor samples has become increasingly important. By identifying adverse genetic markers early in the disease, the risk of metastasis will be reduced and long-term survival rates will increase. Paraffin FISH has been used to identify the clinically relevant copy number variants (CNV) such as the high risk markers: loss of *BAP1* from chromosome 3, loss of 1p

and gain of the long arm of chromosome 8; and the good risk marker: gain of 6p. We have introduced SNP array, which offers a genome-wide screen for detection of all UM CNV. SNP array has the added advantage of demonstrating copy neutral loss of heterozygosity, which may occur in patients who have *BAP1* mutation. Although genetic studies are easily performed on advanced tumors and at enucleation, one of the problems of early diagnosis of ocular melanoma is the small tissue size at vitrector or fine needle sampling. We report our early laboratory experience with extremely small UM biopsies and the use of different procedures to provide sufficient DNA for SNP array.

### Genomewide NIPT Complements SNP Microarray to Confirm Trisomy Rescue Events

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SNP microarray analysis is commonly requested at prenatal diagnosis for high-risk pregnancies. SNP microarray can detect genomic gain and loss, lower levels of mosaicism than conventional karyotyping, and copy neutral regions of homozygosity (ROH). ROH can indicate close common parental ancestry and uniparental disomy (UPD). Recently, noninvasive prenatal testing (NIPT) has been widely accepted as a screening tool for common aneuploidies. NIPT uses fetal (placental) DNA circulating in the maternal circulation. Although NIPT is sensitive and specific, false-positive results occur, with confined placental mosaicism (CPM) involving aneuploidy being a common cause. CPM is commonly associated with intrauterine growth restriction, pregnancy loss, or perinatal death in some cases. CPM can also be a marker for UPD. Four cases will be described where NIPT has indicated a trisomy and subsequent prenatal diagnosis with SNP microarray has detected ROH on the chromosome of interest; a case each of trisomy 16, trisomy 2, trisomy 21, and trisomy 13. Further investigation has confirmed UPD in two cases and has inferred CPM in the other cases. While the cases presented do not involve a chromosome with known imprinted genes, there is a risk of unmasking an autosomal recessive disease and an undetected residual trisomy cell line cannot be excluded.

### EDUCATION, ETHICS AND SOCIAL ISSUES

#### An Educational Framework for Continued Professional Development of Genetic Counselors Through Introduction of Advanced Counseling Workshops

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Continued professional development (CPD) is a routine component of genetic counseling practice to ensure practising genetic counselors maintain their knowledge and skills. To support our genetic counselors in continuing to build their counseling skills, we have developed an educational framework centered around Kolb's theory of experiential learning, which focuses on advanced counseling skills. Through a series of facilitated workshops, counselors engaged in a cycle of activity, reflection, learning, and application aimed to

provide further skills training, an opportunity to increase awareness of counseling theory and applying it to genetic counseling practice. This learning opportunity enabled a large genetic counseling team with a breadth of experience to participate. We describe the process of using an external facilitator (a specialist in counseling) to teach advanced counseling skills and deepen how we integrate these skills into genetic counseling practice. A genetic counselor was assigned to this brief working closely with the facilitator to obtain feedback from participants after each workshop. This was taken on in planning future workshops. At the end of the year, a semistructured questionnaire was administered to participants evaluating whether the workshops had met their CPD learning needs. Participants were asked to consider theoretical content, method of delivery, and application to clinical practice. Suggestions were invited to inform future workshop planning. The outcome of the first year in implementing advanced counseling workshops was valued by the team, as it increased awareness of how we can integrate counseling skills and theory more effectively into our practice. We conclude this experiential learning education framework is beneficial to meet CPD learning needs.

#### Person-Centered Genomics: Experiences of Queensland Genomics Community Advisory Group

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*Background:* Consumer and community engagement has become a priority in health and medical research. To address this priority, Queensland Genomics established a Community Advisory Group (CAG) with dual role of advisory committee and leaders in community-centred activities. *Aim:* To summarize the learnings from a CAG in addressing the challenges regarding community engagement in genomic research and service delivery. *Methods:* The CAG's structure and function were captured by analyzing documentation from Queensland Genomics and the CAG. The experiences of CAG members ( $n = 11$ ) were provided through interviews, group discussions, and written submissions. *Results:* In its advisory capacity, CAG provided advice to some Queensland Genomics projects, contributing to governance review, participating in the project selection process, and designed project reporting on consumer and community engagement. The CAG was provided resources to develop and lead community-focused projects. The CAG Projects address four areas; informing the community, workforce development, supporting genomic consumers, and research from the consumer perspective. The main barrier experienced by the CAG centred on ability or willingness to incorporate CCE in health service planning and projects. This barrier predominately affected the advisory capacity of the CAG. Key enablers for the dual roles of the CAG included; diversity of CAG members' skills and experience, relationships (within CAG, between CAG and Program and CAG member networks), resourcing (financial and human), and the CAG's ability to self-determine their direction. *Conclusion:* When appropriately structured, resourced, and supported, CAGs can effectively identify and lead consumer-focused projects with health implementation programs for genomics.

## Health Interpreter Training in Genetic Terminology: An Update on Delivery and Evaluation

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**Background:** Health Interpreters provide a vital service within the health system for patients with limited English. Language skills in specialist areas tend to come from work-based practise or post-certification professional development. **Aim:** To delivery and evaluation of a training session for Health Interpreters on genetic concepts. **Methods:** In July/August 2020, three 2-hour online training sessions on genetic concepts were held in English with a cohort of Health Interpreters. The training program included presentations on basic and applied genetics, two interactive activities. A recording of training has been edited to a 1-h seminar that is available online. Evaluation of the 2-h training session was undertaken with pre- and post-event surveys and a 6-month follow-up survey. These surveys explored changes in participant knowledge, self-efficacy, attitudes and behaviour, and session experience. **Results:** 118 interpreters participated in the training sessions, and there have been a further 116 views of the recorded seminar. Respondent knowledge improved and gains were maintained at 6 months ( $p < .01$ ). There were no changes in self-efficacy, attitudes, and self-reported practice. Self-reported practice behaviour varied considerably between participants, but was not changed by the training. Most respondents agreed that training was useful (93%) and relevant (79%) to their work. **Conclusion:** Health Interpreters found the training acceptable and demonstrated sustained improvement in knowledge of genetic concepts. Increased delivery of this training and associated research is needed to assess the impact of this educational intervention on patients.

## Collaborative Development of Educational Resources to Support Medicare-Rebated Genomic Testing for Childhood Syndromes/Intellectual Disability (ID)

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**Background:** Medicare-rebated whole exome or whole genome sequencing can now be ordered for eligible patients by pediatricians in consultation with clinical geneticists. Surveys ( $n = 102$ ) and interviews ( $n = 19$ ) of pediatricians identified barriers and facilitators to ordering testing. Resources to assist with delivering results to families were reported as a priority need for pediatricians. **Aim:** Develop resources to enhance pediatricians' knowledge and confidence. **Methods:** Over a 6-month period, we used codesign and stakeholder

feedback to determine the best approach to developing resources for rare genetic conditions. **Results:** A priority list of causative genes for ID was created based on disease frequency per the Decipher database and an audit of online resources. Feedback from pediatricians indicated a preference for resources that would help communicate genomic test results to families and assist with clinical management. Resources were designed to incorporate point-of-care guidance for pediatricians and disease-specific information for families. Iterative review with pediatricians (primary target audience), patient advocates (representing the secondary audience), and rare disease experts including genetic counselors and clinical geneticists yielded a fact sheet template written to a reading age of ~14–15 years. Clinical content experts are using this template to develop ~20 fact sheets with the assistance of a multidisciplinary Review Committee and team members with experience in medical education. Early feedback indicates that this novel approach meets the needs of the target audience. **Conclusion:** Utilising a multidisciplinary team incorporating medical education expertise can generate purpose-built resources quickly and effectively. This approach can be applied to future resource development for genetic disorders.

## Referral Pathways: Integrated Genetic Healthcare for Aboriginal and Torres Strait Islander Queenslanders

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**Background:** Advances in genomic technologies promise to revolutionize healthcare. It is essential we identify barriers to Aboriginal and Torres Strait Islander peoples' engaging with genetic health services. **Aim:** To support Aboriginal and Torres Strait Islander Community Controlled Health Organizations (ATSI CCHOs) of Queensland identify preferences and recommendations for a pathway to sensitive and integrated genetic healthcare. **Methods:** Workshops facilitated across Queensland sought advice from service stakeholders and the community about barriers and enablers to access, quality experience of genetic testing and counseling for Aboriginal and Torres Strait Islander Queenslanders. Thematic analysis identified key themes and informed the development of documentation outlining recommendations to realize a goal of integrated healthcare for ATSI CCHO patients accessing Genetic Health Queensland (GHQ). **Results:** We describe topics and recommendations identified through workshops for core themes: (1) workforce, (2) coordinated care, and (3) public awareness. The penultimate version of the integrated healthcare model will be presented, emphasising the role of co-design and partnership between the public and community-controlled health service sector; describing recommendations for action that support Aboriginal and Torres Strait Islander access to quality genetic healthcare. Participants reviewed and confirmed the Integrated Genetic HealthCare (IGHC) model as inclusive and representative of their advice. **Conclusion:** ATSI CCHOs champion patient access to quality healthcare for Aboriginal and Torres Strait Islander peoples. Partnership between ATSI CCHOs, the public hospital, and health services that is GHQ has enabled development of the pathway and should lead to improved access to sensitive, appropriate, and quality health genetic services for Aboriginal and Torres Strait Islander Queenslanders.



## Developing Capacity in Genomic Medicine Through Implementation Focused Training

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**Background:** Rapid advances in genomic technologies are providing opportunities for significant improvement in clinical care. One major challenge to implementing genomics into widespread clinical care is insufficient capacity in our trained healthcare workforce to facilitate the rapidly increasing availability of genomic technologies. It is imperative that we put frameworks in place to enable genomics for best practice and efficient patient care. **Aim:** The Genomic Institute is a Metro North Health-led initiative that aims to facilitate the mainstreaming of genomic care into the Queensland healthcare system by developing strong and implementable training in genomics practice. **Methods:** There have been considerable efforts, Australia and worldwide, to assess priority areas and methods for genomics training. The Genomic Institute is using this evidence base to implement a training program in genomics, to enable mainstream use of genomics. **Results:** The Genomic Institute educational framework includes genomics foundations training complemented by speciality specific training, initially in renal, maternal fetal medicine, primary care, nursing, and midwifery but also incorporating local needs assessment for future development. The program has successfully integrated partner initiatives and has early indicators supporting high impact. Evaluation is integrated into the programs, to inform future scope and assess the impact and outcomes of the genomics education. **Conclusion:** To fully capitalize on developing genomics technologies, it is essential to mainstream genomics implementation. The Genomic Institute educational program is being developed to facilitate efficient and evidence-based training to ultimately improve the delivery of care and patient outcomes.

## An Ethical Decision-Making Framework for Genomic Testing in Pediatric Kidney Disease

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**Background:** Technological advances and increased access have led to genomics expanding beyond the genetics speciality. As a result, nongenetics specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making around patient selection is required to ensure equitable access while maximising the utility of genomic testing, from a patient and resource perspective. However, there are currently no frameworks to guide decision-making for genomic testing in pediatric nephrology. **Aim:** To develop an ethical decision-making framework to guide patient selection for genomic testing in pediatric kidney disease. **Methods:** A three-staged approach was used: (1) review of the literature on decision-making for genomic testing in nephrology and other disciplines; (2) observations of approaches to genomic testing in the general nephrology clinic and the renal genetics clinic at the Royal Children's Hospital; (3) review and revision of the framework with key stakeholders, including clinical geneticists, genetic counselors, pediatric nephrologists, clinical ethicists, and families from the renal genetics service. The initial framework was modified until

consensus from all key stakeholders was reached. **Results:** A decision-making framework was created. This framework outlined the key decision-making categories and sub-categories for patient selection, with corresponding questions to aid usage. A number of case studies were also developed to demonstrate the framework's application. **Conclusion:** This framework will guide decisions around patient selection for genomic testing in nephrology at the Royal Children's Hospital as well as other institutions and disciplines. In doing so, it will facilitate consistent approaches to genomic testing, to maximize equity and utility.

## Resources for Navigating Genetic Health Services in Queensland: The Patient Communication Toolkit

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**Background:** Through Queensland Genomics' engagement with consumers and the community, health consumers have provided anecdotal evidence which identified that a lack of understanding of precisely 'how' to access genetic testing, contributed to the consumer's diagnostic odyssey. **Aim:** To develop resources that will assist patients and carers in engaging with and accessing genetic and genomic health services and testing in Queensland. **Methods:** Community Advisory Group developed and led the creation of the resources. Drafts of the toolkit were developed by professionals with experience in genetics, health services, and communications. These drafts went through two calls for feedback, which targeted consumer and community and health stakeholders. **Results:** A series of five facts sheets aimed at patients and carers was developed; Introduction to genetics and genomics, Searching for a diagnosis? (accessing genetics testing in Queensland), Your guide to genetics and genomic testing, Clinical Geneticists in Queensland (public and private), and Genetics and Genomics for GPs. The toolkit has been translated into five languages other than English; Arabic, Persian (Farsi), Japanese, Vietnamese, and Chinese (simplified). A promotional campaign has been used to promote the toolkit, both online and through stakeholders' preferred communication methods (i.e. social media, newsletters). **Conclusion:** Engaging community and health service stakeholders in developing patient-focused resources, effectively created informative resources. Research assessing the impact of the resources on health service access and diagnosis, is needed to demonstrate the implications for patients and the value of replicating the toolkit initiative in other health jurisdictions.

## Supporting Families in Clinical Trials

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**Background:** Participation in a pediatric clinical drug trial with an invasive mode of delivery requires significant commitment from participants' families. There is limited literature to inform practice and

ensure families are adequately supported during these trials. *Aim:* To understand parental experiences and the challenges of participating in a long-term pediatric clinical drug trial. *Methods:* A qualitative study was conducted in the form of an anonymized survey sent via a third party vendor. The survey was sent to 16 participants who had been enrolled in the drug trial for >12 months. *Results:* The most important factor influencing parental experience was trust in the trial team. The largest obstacle raised by parents was the mode of drug delivery, a daily subcutaneous injection. The children and their parents found the mode of delivery traumatic at trial commencement. By the end of the first year, families reported the injections had become part of daily routine. Parents reported participation in the trial required significant commitment from the whole family. The frequency of health-related appointments contributed to a level of fatigue affecting their experience. Parents reported functional improvements in their children, which they attributed to the trial. Families felt participation in the trial gave them hope for their child's future. *Conclusions:* The mode of medication administration has a significant impact on parental experience of participation. The early stages of the trial are particularly challenging and families can be supported by providing additional support including holistic care, peer support, coping strategies, and opportunity to provide feedback.

### Implementing Genomic Testing as Routine Care Within Pediatric Settings Using Implementation Science

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*Background:* Australian children with intellectual disability can access genomic testing from pediatricians via Medicare since May 2020. To support the implementation across the state of NSW, complexity science was combined with implementation science and applied through participatory action research. *Aims:* To (1) understand capacity within the system to perform genomic testing for intellectual disability, (2) identify barriers/facilitators to change and assess appropriateness and acceptability, (3) design implementation strategies, and (4) evaluate the impact of strategies on implementation outcomes within genetic and pediatric settings. *Aims 1 and 2: Genetics:* In-depth, semistructured interviews ( $n = 8$  clinical geneticists/heads of department,  $n = 7$  genetic counselors (GC)). *Pediatrics:* Sequential survey ( $n = 102$ ) followed by in-depth, semistructured interviews ( $n = 19$ ). *Aims 3 and 4: Genetics:* survey of processes ( $n = 8$  sites) and focus group ( $n = 8$  heads of departments/clinical geneticists,  $n = 6$  clinical genetics,  $n = 6$  GC). *Pediatrics:* Longitudinal in-depth, semistructured interviews ( $n = 12$ ) with two GCs reporting on multiple sites across NSW. *Results:* Integrating genetic services with pediatric services to perform genomic testing requires significant behavioural changes at the individual level and process changes at the service and system levels. Genomic testing was perceived as appropriate and acceptable by genetics and pediatrics. Environmental restructuring, resources, professional roles, and boundaries were top barriers for genetics services.

Knowledge, skills, intervention complexity, and environmental context and resources were top barriers for pediatricians. Multiple strategies were applied across the system with positive impact on implementation outcomes. *Conclusion:* A complexity science-informed implementation science approach should be applied when introducing genomics into nongenetic settings.

### Parents' Experiences With Being Offered Additional Findings for Their Child With Hearing Loss

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*Background:* From 2016 to 2017, 106 children diagnosed in Victoria with bilateral moderate, severe, or profound hearing loss following newborn hearing screening participated in the Melbourne Genomics Health Alliance Congenital Deafness Project. These children were offered exome sequencing to try to identify the basis of their hearing loss and were also offered additional findings. Parents could choose which types of genetic results they wished to receive: A) hearing loss, B) 'A' plus other conditions that usually develop in childhood that are preventable/treatable, C) 'A'+B' plus some other conditions that usually develop in childhood that are not preventable/treatable. All parents received genetic counseling. *Methods:* We conducted semistructured interviews with parents whose children participated in the study to explore their views about being asked to choose which results to receive and experiences receiving the results. Data were analyzed using inductive content analysis. *Results:* Nineteen parents of 18 children were interviewed, which included parents who had opted for each of the three choices (A = 4, B = 7, C = 7). Two had received additional findings. Many parents found it difficult to decide which types of findings to receive, often feeling the weight of responsibility to make the 'right' decision for their child. Several parents raised concerns regarding their child's future ability to obtain insurance. Despite this, most were grateful they were offered the opportunity to choose with some feeling empowered. *Conclusion:* These findings will be used to refine informed consent and results in delivery processes if and when this testing is offered to children with hearing loss in the future.

### Perceived Heritability of Mental Health Disorders and Attitudes Towards Psychiatric Genetic Testing in Australia, the UK, and USA

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*Background:* Accurate knowledge about heritability is a desired outcome of genetic education campaigns: overestimation of heritability is considered an indicator of genetic deterministic thinking and is associated with negative outcomes such as stigma and discrimination. Underestimation of heritability may indicate motivated rejection of genetics. The relationship between perceived heritability of

mental health disorders and attitudes towards genetic testing for those conditions is unknown. *Aim:* To provide information about intuitive heritability and attitudes towards psychiatric genetic testing in alcohol dependence, schizophrenia, and depression, in a large sample of members of the general public from three different countries. Also, to evaluate the relationship between perceived heritability and attitudes. *Methods:* We surveyed 4,975 members of the general public from Australia, the UK, and the USA, and evaluated attitudes towards psychiatric genetic testing. Participants were asked about their interest in psychiatric genetic testing, perceived usefulness of genetic testing, and beliefs about malleability of behavior, among others. We also asked them to estimate the heritability of alcohol dependence, schizophrenia, and major depression. We used logistic regression to estimate the association between genetic literacy, intuitive estimates of heritability, and sociodemographic variables, on the one hand, and attitudes, on the other. *Results:* We found a high interest in psychiatric genetic testing. There was also a nontrivial percentage of participants with serious concerns related to learning about personal genetic predisposition. We found a significant association between most attitudes and perceived heritability. *Conclusion:* The association between attitudes and intuitive heritability highlights the complexity of learning about genetics.

## GENETIC COUNSELING

### Expanded Carrier Testing at Eugene: Results of the First 1044 Tests

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*Background:* The use of expanded genetic carrier screening is increasing, but information about genetic test and counseling outcomes is lacking, particularly in the setting of couples' testing. *Methods:* Here, we describe our experience of offering expanded genetic carrier screening for 301 autosomal recessive and X-linked disorders, utilizing the Eugene digital genetic counseling platform and the Invitae genetic carrier screening panel. *Results:* Screening was performed in 1044 individuals. Carriers were identified for 224/301 (74%) of the genes tested. Individuals tested were carriers of between 0 and 8 conditions (mean 1.8) with 787 (85%) being carriers of 1 or more conditions. The highest carrier frequencies were for the genes HFE, CFTR, SerpinA, GALT, and BTD, although these included many low penetrance variants that were not actionable in a reproductive setting. 95% of individuals were tested as part of couples' testing, and 498 couples reports were issued, of which 24 (4.8%) were reported as high risk of an autosomal recessive or X-linked condition that was potentially actionable. An additional 71 couples (14%) received increased chance reports for conditions that were assessed as not medically actionable during pregnancy, including 39 for hemochromatosis. 30 (2.9%) of individuals received secondary findings of potential relevance to their own health, most commonly hemochromatosis. *Conclusion:* Expanded carrier testing identifies about 1 in every 20 couples at being at increased risk for a severe autosomal recessive or X-linked disorder. Careful genetic counseling and assessment of couples' results are required to ensure accurate communication of disorder severity and level of risk.

### Exploring Training Needs of New Genetic Counselors in Their Transition from Intake Assistant Roles

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Intake assistants are an increasingly common role seen in many clinical genetic services. Students enrolled in a Master of Genetic Counseling course have routinely been employed as intake assistants for many years at the Parkville Familial Cancer Centre and Genomic Medicine Department (PFCCGM) undertaking tasks and responsibilities aligned with the Australasian Society of Genetic Counsellors Position Statement for Intake Assistants. This group of genetic counselors have a unique transition pathway from a student working within a genetics service to genetic counselor. To better understand the education, training, and support needs of graduate genetic counselors during their transition period from intake assistant to genetic counselor, an anonymous mixed methods survey will be administered to eligible participants. Participants will include genetic counselors currently employed at the PFCCGM who have previously been employed as an intake assistant. We anticipate results will identify the training and support needs of those transitioning from intake assistant to genetic counselor. We will present the benefits and challenges of transitioning from intake assistant to genetic counselor. This data will be utilized to structure a training and on-boarding programme that pre-emptively meets the needs identified. This survey may also prove a useful foundation for future research into the support needs of new genetic counselors.

### How Do Translocation Carriers and Their Partners Experience Noninvasive Prenatal Testing to Detect Unbalanced Translocations?

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*Background:* Carriers for balanced chromosome translocations have an increased chance of passing an unbalanced translocation to their children. Little is known about how couples adapt to this information and make reproductive decisions. Victorian Clinical Genetic Services has offered noninvasive prenatal testing (NIPT) to carriers of balanced reciprocal translocations since 2015. *Aim:* To explore the experience of couples having NIPT to detect unbalanced translocations and to understand their motivations for choosing this option. *Methods:* Semistructured interviews were conducted with translocation carriers and their partners. Purposive sampling based on the participant's geographic location, requesting practitioner speciality, and NIPT result was used to capture a range of experiences. Interviews covered the impact of being identified as a translocation carrier, motivation for accepting testing, and perceived benefits and risks. Interview transcripts were analyzed using thematic analysis until consensus in coding was reached. *Results:* Thirteen people from 10 couples took part. Participants welcomed NIPT to screen their pregnancy for an unbalanced translocation, felt they had benefited from speaking to an expert about their translocation and recalled having sufficient confidence in the result to decline a diagnostic testing procedure. Participants had diverse experiences accessing cytogenetic testing for their children for carrier status of the reciprocal



translocation (information not available from NIPT). *Conclusions:* The complex psychosocial impacts of carrying a balanced translocation highlight the importance of access to genetic counseling. Accurate assessment of reproductive risk and information about the benefits and limitations associated with NIPT should be provided to ensure couples are well supported.

### The Complexity Around Mosaic Embryo Decision Making — A Genetic Counseling Perspective

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*Background:* Our genetic counseling team have reported mosaic results to >250 patients since the beginning of 2020, and there is an upward trend in patient interest, and willingness to consider transfer. As patients continue to request the transfer of mosaic embryos, and research advances regarding transfer outcomes, it is critical the genetic/medical professionals who counsel these patients are aware of the complex factors that feed into important decision making. *Aim:* To explore genetic counseling perspectives on counseling issues for patients considering transfer of a mosaic embryo, including barriers, commonalities, and themes that impact their decisions. *Methods:* Fundamental thematic analysis on genetic counseling consultation notes detailing questions, concerns, motivations, and decision outcomes was utilized for gaining a preliminary perspective. Specific case vignettes help highlight the complexity of these decisions. *Results:* Depending on the result, patients with PGT-A NGS reported mosaic embryo(s) have the option to consider a transfer, retaining, or discarding these embryos. Thematic analysis revealed themes regarding factors that influence decision-making. *Patients less likely to proceed with embryo transfer:* highly risk averse, poor management of uncertainty, perceived limited options, lived experience of unhealthy pregnancy or birth (i.e., family/friend), complex reproductive history, and high emotional burden of the decision. *Patients more likely to proceed with transfer:* extensive fertility journey, high level of information comprehension, encouraging community support, low emotional burden of the decision, and awareness of age-related limitations (ie. maternal age-related aneuploidy). *Conclusion:* Our work highlights the potential benefits of a genetic counseling guideline of factors to present/challenge to patients.

### The Role of the Genetic Counselor in Pediatrician Ordered Genomic Testing

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*Background:* In Australia, Medicare item numbers for genomic testing were introduced for childhood syndromes/intellectual disability in May 2020. These allow pediatricians to order genomic tests for eligible pediatric patients in consultation with a clinical geneticist. *Aim:* To illustrate how the unique skillset of the genetic counselor is essential in both supporting pediatricians to arrange genomic testing and ensuring patient care in a changing health landscape. *Methods:* Two genetic counselors from the Genetics of Learning Disability service used the express model reinforce change approach to facilitate pediatrician ordered genomic testing across multiple sites

in NSW. This involved education provision to pediatricians through a series of webinars, demonstration of pre and post-test genetic counseling in joint clinics, and reinforcement of behavior change by providing ad hoc clinical support as pediatricians moved to independently order this testing. Both genetic counselors participated in fortnightly interviews to record their experiences with this process, including barriers and facilitators. *Results:* Genetic counselors can mitigate the barriers to the successful uptake of pediatrician ordered genomic testing, resulting in pediatricians independently ordering tests across multiple sites. Genetic counselors can increase pediatrician capability in genomic knowledge (e.g., consent/ counseling skills) via a variety of formats, assist in navigating the logistics of sample collection and testing, and aid in the provision of information to patients and families. *Conclusion:* As genomic technologies continue to evolve and Australian health policy promotes ordering of genomic tests by nongenetics health professionals, genetic counselors can play a key role in the safe, and equitable adoption and delivery of this testing.

### Exploring the Journey to Genetic Services: A Qualitative Study of Parental Perspectives of Children With Rare Disease

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*Background:* Approximately 80% of rare diseases are thought to be genetic in etiology. Individuals with these conditions often experience extended diagnostic delays, typically associated with heavy financial and psychological costs. Uptake of genetic services is limited, and little is known about the barriers and facilitators to service access in Australia. Understanding the experience of the diagnostic journey for rare disease is essential to improve and facilitate access to genetic services. *Aims:* Explore the current experience of the diagnostic journey for parents of children with rare disease in Queensland and Victoria. *Methods:* Parents of children with rare disease were recruited through the support group, Syndromes Without A Name. Semistructured interviews explored the experience of the diagnostic journey. Interviews were transcribed verbatim and thematically analyzed. *Results:* Twenty-four interviews were conducted, and four main themes were developed: (1) The value of diagnosis (2) Uncertainty permeates all aspects of the diagnostic journey, including post-diagnosis (3) Parents became advocates, experts, and care co-ordinators for their child out of necessity (4) Parental concerns were not taken seriously and parental expertise often unacknowledged. When asked about recommendations for improving the diagnostic experience, parents described referral guidelines, educational tools, and improved care coordination. Moreover, throughout interviews participants emphasized the importance of forming partnerships between parents and healthcare professionals (HCPs). *Conclusions:* Our findings highlight areas for improving the diagnostic journey for rare disease. We also emphasize the need for educational resources to support parent and HCP awareness of and access to genetic services for children with rare disease.

## Atypical Results from Genomewide NIPT for a Carrier of a Balanced Translocation

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**Background:** Noninvasive prenatal screening (NIPT) is considered a superior primary prenatal screen for common aneuploidy. For balanced translocation carriers, genomewide NIPT (gw-NIPT) is a clinically relevant and practical option. As gw-NIPT becomes integrated into routine practice and broadens in scope, it is important to remain aware of limitations possible complex results and the continued relevance of prenatal diagnosis. **Aim:** Our service offers gw-NIPT to balanced translocation carriers who meet certain criteria. We present a case study detailing unexpected results and subsequent counseling, investigations, and outcomes. **Results:** A gw-NIPT result for a carrier of a balanced translocation indicated trisomy 6. This was suggested to have arisen from malsegregation of a maternal translocation. Viability at 11 weeks and normal obstetric ultrasounds at 12 and 16 weeks suggested confined placental mosaicism arising from a post-zygotic rescue. Microarray from amniocentesis indicated no chromosomal imbalance, although detected maternal UPD 6 and regions of isodisomy. Ongoing obstetric management was arranged in the context of intra-uterine growth restriction. Multiple genetic counseling interactions were required to facilitate communication and comprehension of these complex genetic concepts, and counseling issues adapted alongside changing concerns. **Conclusion:** For balanced translocation carriers, gw-NIPT has practical clinical utility. However, complex gw-NIPT results often require ongoing consultation between genetics services, laboratory, and high-risk obstetrics. Awareness of this, as well as the biological limitations which constrain gw-NIPT mean that ultrasound and prenatal diagnosis remain important investigative tools.

## 'We're All Different. But We're All The Same' — Listening to Caregivers' Voices When Designing a Rare Genetic Epilepsy Family Conference

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This study aimed to explore the preferences of parents of children with rare genetic epilepsies (RGEs) for a genetic counselor organized family conference. RGEs are typically severe and complex conditions which create significant psychosocial challenges not only for the child, but the whole family. Parents of children with RGE have a wide range of support and information needs. It has been suggested that family conferences are one approach to meet these needs while potentially empowering parents and reducing psychological stress. However, little is known about parents' preferences with regards to family conference design and content. A qualitative approach using semistructured focus group interviews was used to explore the preferences and opinions of nine parents of children with RGE attending Sydney Children's Hospitals Network regarding the planned 2021 RGE family conference. Findings revealed that parents collectively shared a strong desire to network in-person with other parents of children with RGE, especially with those whose children were of similar ages. Thematic analysis highlighted a need to normalize the unique form of grief associated with caring for a child

with a rare genetic epilepsy. Preferences for content included hearing other families' journeys, navigating government systems, and learning about RGE therapies and advancing clinical research. This study has informed the structure of our upcoming parent-centered family conference. It provides insight into the wide-ranging psychosocial needs of parents' of children with rare genetic epilepsies. Findings highlight that RGE parents value the importance of face-to-face networking with peers, even in the pandemic era.

## A Survey of Patient Satisfaction with a Clinical Genetics Service

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**Background:** Although there is no consensus on exactly what or how to measure patient satisfaction, it has become an integral part of assessing health care delivery. National standards state that health services monitor patient satisfaction and use the outcomes to set realistic goals for improving partnerships between clinicians and patients. **Aim:** To develop and administer a purpose-designed survey to assess patient satisfaction of patients who attended a Victorian Clinical Genetics Services (VCGS) clinic and identify areas for service improvement. **Method:** The survey was developed following a review of existing patient satisfaction surveys in Australia. The final survey contained questions from the Australian Hospital Patient Experience Question Set which were adapted for outpatient use, the Genomics Outcome Scale and a series of purpose-designed service-specific questions. An online survey was developed using the RedCap survey tool which was piloted on 12 patients. The survey was sent by email to all patients seen at a VCGS Royal Children's Hospital or regional clinic during February and March 2021. **Results:** 606 surveys were sent, with 89 returned to date (an initial response rate of 14.7%). 93% of respondents were parents of a patient, with the remainder being patients themselves. Preliminary analysis of the current data shows that approximately 50% of appointments were by telehealth, 93.4% of patients rate the overall quality of care as good or very good, and 89% would recommend the service to a friend. Data collection is ongoing, and results from the final dataset will be presented.

## The Experiences and Needs of Individuals With MNF And FTD, and Their Family Members, Towards Genetic Counseling and Genetic Testing

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**Background:** Genetic counseling and diagnostic genetic testing is becoming increasingly routine in motor neuron disease (MND) and/or frontotemporal dementia (FTD) care due to the emergence of genotype-driven therapy trials. There are currently no consistent, evidence-based genetic counseling approaches to diagnostic testing in MND/FTD. **Aim:** Explore patient and family members' diagnostic testing and counseling experiences and generate recommendations to inform care in future. **Methods:** Interpretive description

methodology was used. Semistructured interviews were conducted with MND/FTD patients and family members either by audio or text, one-on-one or conjoint (depending on participant preference). Advertising occurred through Australian MND and FTD organizations. Themes were developed using inductive thematic analysis. *Results:* Eighteen individuals from 13 families participated. Diagnostic testing occurred alongside other MND/FTD disease burdens due to progressing disease. Testing pathways varied and were informed by local health system characteristics; some were barriers to a positive genetic counseling experience. Interactions with health professionals and MND/FTD association staff that included open communication, time to facilitate adjustment, and address questions led clients to feel supported and informed regarding testing and sharing information with other family members. Individual and family characteristics informed the level of information and support required. *Conclusion:* A supportive, informative genetic counseling process adapted to the client's unique needs must be facilitated, and testing pathways must be clarified and consistent. Guidelines to inform best practice are likely to be beneficial. These improvements could reduce some of the burdens of the disease lived experience by improving access to and quality of genetic counseling provided across Australia.

### Understanding the Introduction and Evolution of Percept Noninvasive Prenatal Testing Results in Victoria

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*Background:* Since the introduction of noninvasive prenatal testing (NIPT), there has been rapid evolution in clinical practice and an increase in the range of conditions which can be detected beyond the common autosomal trisomies and sex chromosome aneuploidy. *Aims:* This study aimed to understand the changes in NIPT since its introduction through exploring healthcare provider (HCP) experiences and one NIPT laboratory's testing data. *Methods:* A mixed-method approach was used. (1) Key-informant interviews were undertaken with HCPs with at least five years' general NIPT experience. Interviews were transcribed verbatim and analyzed using inductive content analysis. (2) A clinical audit of Percept (Victorian Clinical Genetics Services branded NIPT) with descriptive analysis of result types (2015-2020). *Results:* To date, five HCPs have been interviewed; genetic counselors (2), clinical geneticist (1), obstetrician (1), general practitioner (1). HCPs described workload and role changes since NIPT's introduction to clinical practice due to increasingly complex NIPT results. Counseling patients required longer appointments, more preparation, and involvement by the genetics HCP. Analysis of 74,550 records for Victorian women who had Percept NIPT supported reported HCP experiences of NIPT, with complex results (rare aneuploidy, unbalanced translocations, and segmental imbalances) forming an increasing portion of results: 0.4% (2015) to 1.1% (2019). *Discussion:* Whilst NIPT has improved prenatal screening for chromosome conditions, leading to a greater number and range of

severe conditions identified, HCPs require greater resourcing and support for changing caseloads due to complex NIPT results

### Scenario-Based Responses to Hypothetical Fetal Diagnosis By Noninvasive Genetic Testing

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*Background:* Cell-free fetal DNA (cfDNA) is now a commercially available test which has been used in noninvasive prenatal testing (NIPT) to detect single gene disorders. What women would do with this information on a population screening level (in a scenario where a person had no lived experience of these conditions from a known family history) is yet to be explored. *Aim:* To discuss several genetic conditions that could be detected with single gene NIPT with women to explore attitudes toward termination of pregnancy for these conditions. *Methods:* Several genetic conditions were described without being named, including neurofibromatosis 1 (NF1), Duchenne muscular dystrophy (DMD), Hereditary breast and ovarian cancer syndrome (HBOC), 22q11 deletion syndrome, Turner (XO) syndrome, and Huntington's disease (HD). Scenarios such as a healthy carrier and an incidental finding were also included. An online survey was carried out with 219 female participants from Western Australia. The scenarios were not named to avoid any preconceived ideas about the conditions. *Results:* The highest response for whether to end a pregnancy at gestation up to 18 weeks was for the DMD scenario described, followed by HD, 22q11 and then NF1. A healthy carrier, Turner syndrome, incidental findings, and HBOC had relatively low rates of women agreeing they would end a pregnancy, but there was still a proportion of women who would end a pregnancy in these circumstances. *Conclusion:* Screening a population for rare genetic disorders would be expected to increase the termination rate and require widespread genetic counseling.

### GENETIC EDUCATION

#### Development of Decision Aids to Support Mainstreaming of Genomic Testing in Renal Medicine

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*Background:* As technologies advance, knowledge grows, and costs decrease, genomic testing is increasing in value as a diagnostic tool for patients, including those with kidney disease. Mainstreaming of genomic testing brings value to the patient as they receive their testing from their primary clinician early in their diagnostic journey. However, there is evidence that nongenetic specialists have limited proficiency and confidence in selecting, ordering, and interpreting genomic tests. Clinical decision aids can support the nongenetic specialist in these processes. *Aim:* Develop clinical decision aids to



support the adoption of genomic testing as a diagnostic tool in renal services across Queensland. *Methods:* A project team comprising a nephrologist (AM), clinical geneticist (CP), and a genetic counselor (LF) developed content for a series of decision aids. Content was adjusted based on potential user feedback. An iterative review process aligned the material with human factors and graphic design principles. *Results:* Decision aids to support mainstreaming of genomic testing for genetic kidney disease were developed. Topics included: identification of potential genetic kidney disease patients; key clinical diagnostic features for the different genetic kidney disease subtypes; family history queries; identification of appropriate genomic test panels; processes for requesting tests; and an overview of result interpretation. Contact details for an MDT where expert support can be accessed were provided. *Conclusion:* This series of decision aids were positively reviewed by renal specialists and are expected to support mainstreaming of diagnostic genomic testing in renal medicine. These aids could guide the development of similar aids for other clinical specialties.

## GENETIC EPIDEMIOLOGY

### The Epidemiology of Hereditary Pancreatitis in South Australia

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*Background:* Hereditary pancreatitis (HP) is a debilitating condition caused by the inheritance of a variety of genetic mutations. HP results in inflammation of the pancreas from a young age, chronic abdominal pain, and dependency upon pain management opioids. Severe cases of HP are candidates for total pancreatectomy and islet auto transplant (TP-IAT) surgical treatment. *Aims:* This project is the first to identify Australian families suffering from HP and assess the correlation between phenotypic disease outcome and genotypic variant. *Methods:* Patients with HP were identified from existing hospital records and interviewed for phenotype. Salivary biosamples were obtained from patients and family members to be whole-exome-sequenced (WES) and analyzed in silico using bioinformatics toolkits (GATK). *Results:* A total of 5 pedigrees and 4 individual probands comprising 47 individuals were recruited for the project. Four families possess the mutation *PRSS1* (3 family with R122H, 1 family with A86T). In total, 23 *PRSS1* and 9 *SPINK1* variant carriers across multiple generations were identified, 13 of which self-identified as Indigenous Australian. Our estimated prevalence of HP in South Australia is much higher than the value of 0.1–0.3/100,000 previously described in European populations. Bioinformatics analyses of WES genotypic data yielded three potentially pathogenic variants identified outside of known HP-associated gene: *ECE1*, *GJA5*, and *SPTBN5*. *Conclusions:* The study described the prevalence of HP in an Australian population for the first time, highlighted the importance of utilizing genetic studies to guide medical decision-making in HP, and successfully established a patient database for candidates of TP-IAT treatment.

## GENOMICS

### What Do the General Public Think About Clinical Genomics?

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*Background:* Genomic testing has typically been employed in the fields of rare disease and cancer. However, as genomic sequencing becomes more readily available in mainstream healthcare, the general population is more likely to be exposed to genomics. Therefore, how the genomic uninformed public perceives clinical genomic testing is paramount. This knowledge will be essential in responding to key concerns of the public and allowing for efficient implementation of clinical genomics into wider healthcare. However, most studies have focused on the perceptions of the genomic informed. *Aim:* To investigate the genomic naïve public's perceptions of clinical genomics and clinical genomic testing. *Methods:* MEDLINE, PubMed, and Web of Science databases were searched generating 1612 articles in total. Narrative synthesis was used to extract thematic data along a person's decision-making pathway. *Results:* Twelve full-text articles were included in the final analysis. Most of the studies used questionnaires to determine attitudes of the public towards clinical genomics ( $n = 9$ ). The US conducted the most studies ( $n = 4$ ), followed by Japan ( $n = 2$ ). Themes identified included: pre-exposure perceptions of clinical genomics (e.g., sources of information, influences on decision to undertake genomic testing), personal values and beliefs and implications of undertaking genomic testing, and fear of discrimination. *Conclusion:* The current literature surrounding the perceptions of the genomic naïve public is scarce. The studies analyzed to demonstrate the uncertainty and inconsistencies in the area and the importance of considering cultural contexts among other factors when discerning attitudes towards clinical genomic testing.

### illumina Clinical Services Laboratory (ICSL) Framework Designed to Improve the Evaluation and Reporting of Incidental Findings in Clinical Genetic Tests

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Incidental findings (IFs) present challenges for laboratories and clinicians, as accepted recommendations for evaluation or reporting are lacking. Additionally, protocols for handling IFs can be subjective, time consuming, and difficult to scale. ICSL offers clinical whole genome sequencing (cWGS) with a policy of reporting IFs which may impact medical management. We have developed and validated a framework to streamline the evaluation of IFs and improve consistency in reporting. Stopping points at which an IF may be deemed reportable or not were first defined. For single nucleotide variants (SNVs) impacting single genes, the following criteria must be met: (1) the strength of the gene-disease relationship is classified as 'Strong' or 'Definitive' according to the ClinGen protocol, (2) the variants are classified as likely pathogenic (LP) or pathogenic (P), and (3) the variants are in the correct zygosity. Next, a threshold

was set for ClinGen actionability scores to qualify IFs for reporting. Finally, if actionability scores were insufficient or unavailable, a literature search was performed to identify interventions, screening guidelines, or circumstances to be avoided by carriers. Heterozygous LP or P copy number variants (CNVs) expected to produce a phenotype, or variants of unknown significance (VUS) gains  $\geq 1$  Mb and losses  $\geq 500$  kb were also reported as IFs. Several questions remain unanswered, for example, reporting of risk factors and IFs in individuals who opt out of SFs. Nevertheless, for laboratories offering cWGS, this framework will streamline analysis and bring consistency and transparency to reporting IFs.

### Modern-Day Reproductive Carrier Screening: The Dynamic Nature of Variant Interpretation and the Impact on Risk Interpretation and Clinical Management

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**Background:** Reproductive carrier screening raises unique questions related to variant reclassifications because variants of uncertain significance (VUS) are not routinely reported in this context, and there are time constraints around pregnancy planning and management. Here, we review the extent and timing of variant reclassification in a large clinical cohort and discuss potential clinical management implications of this reclassification. **Methods:** Carrier screening was performed by next-generation sequencing with deletion and duplication analysis of up to 301 genes, and only pathogenic or likely pathogenic (P/LP) variants were originally reported. Clinically significant reclassifications and their timing were identified. **Results:** Out of 126,424 patients included in this analysis, 4,179 (~3.3%) had at least one clinically significant reclassification with an average time to reclassify of 286 days. In this cohort, 418 patients had partners who also underwent testing. Only four patients with a reclassification became 'at-risk' after reclassification (~0.1%). **Conclusions:** Although reclassifications occur infrequently in carrier screening, they can have significant clinical and psychosocial implications for patients and clinicians. A clear consensus on how to perform this reanalysis and provide updates to patients and clinicians is not available yet. As this issue continues to impact carrier screening, both the reporting laboratories and the clinician will have roles in communicating and managing the impacts on patient care. Additional studies are needed to continue to understand the impact on both clinicians and patients of receiving reclassified variant information and also to inform laboratory standards for reclassifying variants in reproductive carrier screening.

### Ontoclick: A Web Browser Extension to Facilitate Biomedical Knowledge Curation

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The world's biomedical literature has achieved a scale that the human brain cannot possibly process. Computers could assist with searching through this vast sea of knowledge, but this requires 'knowledge curation', converting unstructured text into well-defined units of information, such as a set of Human Phenotype Ontology

terms, that a computer can process. Knowledge curation can be a repetitive and laborious process but without knowledge curation, vast amounts of knowledge in the biomedical literature will remain untapped. The paucity of user-friendly tools is one of the reasons for the lack of widespread adoption of good biomedical knowledge curation practices. Here, we present Ontoclick, a web browser extension that streamlines the process of annotating a text span with a relevant ontology term, a key component of knowledge curation. We hope this tool will make biocuration more accessible to a wider audience of biomedical researchers.

### Spinal Muscular Atrophy Diagnosis and Carrier Screening From Whole Genome Sequencing Data

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Spinal muscular atrophy (SMA), caused by loss of the *SMN1* gene, is a leading cause of early childhood death. The American College of Medical Genetics and Genomics recommends SMA carrier screening be offered to all couples either before conception or early in pregnancy. Due to the near identical sequences of *SMN1* and *SMN2*, analysis of this region is challenging. We developed a bioinformatics method, SMNCopyNumberCaller, that accurately identifies the copy number (CN) of *SMN1* and *SMN2* using whole genome sequencing (WGS) data. We characterized *SMN1* and *SMN2* in 12,747 genomes, identified 1568 samples with *SMN1* gains or losses and 6615 samples with *SMN2* gains or losses, and calculated a pan-ethnic carrier frequency of 2%, consistent with previous studies. Additionally, 99.8% of our *SMN1* and 99.7% of *SMN2* CN calls agreed with orthogonal methods, with a recall of 100% for SMA and 97.8% for carriers, and a precision of 100% for both SMA and carriers. By developing SMNCopyNumberCaller using multi-ethnic samples, we were able to identify higher genetic variability in Africans and exclude variable sites that cannot reliably differentiate *SMN1* from *SMN2*, thus optimizing accuracy across all populations. To make SMNCopyNumberCaller useful in clinical settings where WGS is the preferred testing modality, we created a visualization tool that produces static images that represent the data to QC the calls. SMNCopyNumberCaller enables SMA testing to be offered as part of a comprehensive test in neonatal care, carrier screening, and other clinical settings where WGS may be indicated.

### Efficacy of First-Line Gene Panel as Screening Prior to Whole Genome Sequencing in the Diagnosis of Inborn Errors Of Immunity

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**Background:** Inborn errors of immunity (IEI) are rare diseases resulting from pathogenic variants in genes regulating immune function, which are curated by the International Union of Immunological Societies (IUIS). While next generation sequencing (NGS) has significantly improved the diagnosis of IEIs, it is costly and slow. Currently, there are uncertainty regarding whether patients should

undergo initial screening with an IUIS gene panel or proceed directly to clinical exome sequencing (CES) or whole genome sequencing (WGS). *Aim:* To determine the clinical utility of an IUIS gene panel-first approach compared to direct CES/WGS. *Method:* Between 2016 and 2017, 56 suspected IEI cases from the Clinical Immunogenomics Research Consortium Australasia (CIRCA) cohort underwent first-line WGS. A likely pathogenic/pathogenic (ACMG Class 4/5) variant was found in 12/56 (21%) of cases and variants of uncertain significance (VUS) in 5/56 (9%) of cases. We retrospectively reviewed these 17 variants in the setting of the current existing diagnostic methodology of two leading commercial vendors offering abridged IUIS gene panels to determine if they would have been identified by a panel-first approach. *Result:* We found a gene panel-first approach would have identified 10/12 likely pathogenic/pathogenic variants and 3/5 VUSes in panels provided by both vendors. *Conclusion:* First-line screening with an abridged IUIS gene panel is a cost-effective method for detecting clinically relevant variants in suspected IEIs. CES/WGS should be considered for the remaining unsolved cases. This two-tiered approach to testing may have clinical utility by providing a cost-effective way to expedite the genetic diagnosis of IEIs.

### **ATAD3 CNVs and Severe Lethal Mitochondrial Disease: Genotype-Phenotype Correlations and Functional Genomic Strategies for Diagnosis**

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*Background:* The *ATAD3* locus comprises three highly homologous genes (*ATAD3C*, *ATAD3B*, *ATAD3A*) encoding mitochondrial proteins implicated in cholesterol metabolism, mitochondrial DNA homeostasis, and morphology. Recessive deletions or dominant duplications cause lethal mitochondrial disorders characterized by pontocerebellar hypoplasia or cardiomyopathy, respectively. In our experience, the *ATAD3* locus has emerged as the most common cause of lethal perinatal mitochondrial disease, but the repetitive sequence at the locus means diagnoses may be missed or misinterpreted using current genomic strategies. *Aims:* To evaluate genotype-phenotype correlations and techniques for screening *ATAD3* variants by characterizing molecular rearrangements in patients with novel *ATAD3* CNVs. *Methods:* Whole genome and exome sequencing; long read sequencing (ONT); microarrays; RNA studies; quantitative proteomics; biochemical analyses. *Results:* We recently identified 17 individuals (16 families) with a lethal neonatal

presentation including cardiomyopathy, lactic acidemia, and corneal clouding/cataracts due to recurrent *de novo* 68 Kb *ATAD3* duplications (Frazier *et al.*, 2021 *Med*, 2:49-73). The duplications all generated identical chimeric *ATAD3A/ATAD3C* proteins, which appeared to act dominantly, altering *ATAD3* complexes and mitochondrial complex I activity in heart. Our genomics investigations have since uncovered additional subjects with novel *ATAD3* CNVs. These include benign biallelic deletions, along with recurrent *ATAD3* duplications plus a second *ATAD3* CNV that can ameliorate the severe lethal presentation. Functional screens to evaluate *ATAD3* expression (quantitative proteomics) and *ATAD3* complex assembly (blue native-PAGE) showed promising results in validating pathogenic variants. *Conclusion:* Novel *ATAD3* CNVs require extensive functional studies to unravel the complex molecular changes and contribution to pathogenicity, with several promising strategies emerging.

### **Pharmacogenomic Testing: Perception of Clinical Utility, Enablers and Barriers to Adoption in Australian Hospital Settings**

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*Background:* Pharmacogenomic tests can be used to detect variants that affect drug metabolism and predict patients' responses to medications. Despite anticipated benefits to patient care, implementation of pharmacogenomic testing in Australia is limited. *Aim:* This study aimed to assess health professionals' perceptions of pharmacogenomic testing, including attitudes to testing, and potential barriers or enablers, in three Australian hospital settings. *Methods:* An online survey (10–12 mins, 31 multiple choice and short answer questions) was adapted from published measures to assess health professionals' usage, knowledge, confidence, and experience with pharmacogenomic testing, and their perceptions of benefits, risks, and barriers to its implementation. *Results:* Health professionals involved in prescribing decisions across three NSW hospitals ( $N = 103$ ; 70% physicians; 23% pharmacists) completed the survey between July 2020 and May 2021. Although most health professionals (79%) thought pharmacogenomic testing had clinical utility and relevance to their practice, only 33% had used or intended to use pharmacogenomic testing to guide prescribing decisions. A primary barrier to use was a lack of knowledge about pharmacogenomic testing, including when and how to test and the interpretation of results. Absence of guidelines and a perceived scarcity of accessible evidence-based information were additional barriers. Few (47%) respondents reported receiving education in pharmacogenomics. Guidance from institutional experts was perceived to increase the likelihood of using pharmacogenomic testing to inform prescribing decisions in future. *Conclusion:* Further education, development of guidelines, and onsite expert advice could help improve the implementation and adoption of pharmacogenomic testing into routine clinical care to inform prescribing decisions.



## The Utility of RNA-Sequencing in the Study of Muscle Biology and Neuromuscular Disease

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**Background and Aims:** RNA sequencing is a powerful massively parallel sequencing (MPS)-based technology used to interrogate the impacts of likely pathogenic mutations and identify potentially diagnostically useful abnormal transcripts in the rare disease setting. Our study aimed to assess the strengths and limitations of RNA-seq in the context of neuromuscular disease diagnostic work and research aimed at furthering our understanding of fundamental muscle biology. **Methods and results:** Mapping and coverage analyses of new and existing control short read foetal and mature muscle RNA-seq data sets and in silico modeling showed that a significant number of clinically relevant genes contained regions with far from optimal sequencing coverage due to poor mappability using current short-read methodologies, potentially resulting in missed diagnostic opportunities. We also found strong positional bias in short-read RNA-seq datasets and demonstrated that clinically relevant genes were disproportionately impacted by this bias, with a variety of effects on downstream calculations. In addition, a Nanopore (long read) sequencing study of mouse striated muscle showed no evidence of positional bias in reads mapping to mouse genes. Further optimization in mouse muscle and extension into direct (native) long read RNA-seq are ongoing. **Conclusion:** Overall, our study has provided novel insights into fundamental muscle biology and the clinical utility of muscle RNA-seq, affirming established and emerging RNA-seq technologies as powerful tools in the study of neuromuscular disease.

## Pathogenic Variants in Hereditary Cancer Syndrome Genes are Prevalent Among Breast Cancer Patients Not Meeting Various International Genetic Testing Guidelines

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**Background:** Clinical management options have expanded for patients harboring pathogenic variants (PVs) in cancer predisposition genes. Historically, testing costs and clinical implementation challenges led to restrictive testing guidelines in many countries. Increasing evidence demonstrates that broader testing is a cost-effective way to identify patients with PVs. We assessed the efficacy of multiple international testing guidelines in identifying breast cancer (BC) patients with clinically actionable PVs. **Methods:** We reanalyzed a prospective cohort of U.S.-based, primarily Northern European, BC patients, referred for germline genetic testing (PMID: 30526229). We applied testing guidelines from Australia, UK, and two Canadian provinces (Ontario, British Columbia) to this cohort to determine their sensitivity for selecting patients with PVs in high risk (>4x risk compared to general population) breast/ovarian cancer genes. These populations were chosen because of similar healthcare systems and ancestral distribution. **Results:** Over 75% of patients in each country/province analyzed were OOC. Rates of PVs were similar between IC and OOC patients across countries. Existing Canadian, Australian, and UK criteria missed up to 30% of patients with high-risk PVs. The majority (>80%) of PVs in OOC patients were in genes with published management guidelines. **Conclusions:** In our cohort, select international testing criteria identified <30% of patients with PVs. These data suggest expanding certain international guidelines would allow better identification and improved management for BC patients across the globe.

## Clinical Utility of Genetic Testing in Children with Seizure Onset After 2 Years of Age

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**Background:** Seizure disorders secondary to neurologic and metabolic disorders are some of the most common genetic disorders presenting in childhood. A molecular diagnosis in these patients allows for etiologically based treatment and management; therefore, it is critical to maximize the diagnostic yield. ‘The Paediatric Epilepsy? Look Beyond’ is a sponsored program offering genetic testing to patients with epilepsy in Europe and the Middle East. **Aim:** To determine the overall molecular diagnostic yield in pediatric epilepsy patients between 2 and 5 years of age and assess the impact on diagnosing neuronal ceroid-lipofuscinosis type 2 (CLN2) given the opportunity to treat these patients with enzyme replacement therapy. **Methods:** 541 patients were tested using a comprehensive next-generation sequencing (NGS)-based epilepsy panel. Patients were age 24–48 months at the time of testing, had the first seizure at 24 months or over, and had at least one additional finding (EEG, MRI abnormalities, speech delay, or motor symptoms). **Results:** A genetic diagnosis was established in 115 patients (21.3%). CNVs accounted for 16% of diagnosed patients, with 28% being intragenic. CLN2 cases received a molecular diagnosis at an average age of 3 years 11 months, 1–2 years earlier than natural history data. At least 72 (62.6%) patients who received a molecular diagnosis had a disorder that has a targeted treatment, evidence for optimizing pharmaceutical treatment, or on-going clinical trials available. **Conclusion:** This genetic testing program demonstrates the clinical utility of a comprehensive epilepsy gene panel with high-level CNV detection for patients whose first seizure occurs at or after 2 years of age.

## Utility and Diagnostic Yield of Whole Exome Sequencing in Adult Patients with Intellectual Disability

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**Background:** Previous genetic testing for intellectual disability (ID) was often limited to conventional or molecular karyotype and testing for fragile X. Recent accessibility to whole exome sequencing (WES) has facilitated the re-evaluation of monogenic diagnoses for patients with ID who are now adults. A vast amount of literature examining WES in pediatric populations exists, however there is a paucity of literature regarding adult patients with ID. **Aim:** To understand diagnostic yield of WES in adults with ID and clinical and personal utility of testing outcomes. **Methods:** A clinical audit of adult patients who presented to our service between 2018 and 2020, and received WES testing for ID. Each case was reviewed to assess the outcome of genetic testing as well as the clinical and personal utility of results. **Results:** Eight (29%) received a molecular diagnosis that matched their phenotype, 9 (32%) had a variant of unknown significance (one with high clinical suspicion) and in the remaining 11 (39%) cases, a molecular diagnosis was not identified. Incidental carrier status of recessive conditions was identified in several individuals. **Conclusions:** The clinical utility of a genetic diagnosis for adults with ID is often thought to be limited, although important for siblings. Personal utility for patients and their carer(s), following a long diagnostic odyssey is often important and

beneficial. We present cases of interest including one case in which a genetic diagnosis resulted in change to medical management, and a second case in which a genetic diagnosis did not change medical management however facilitated efficacy of social support.

### Mitochondrial DNA Analysis Increases Diagnostic Yield in Patients with Inherited Retinal Disease

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**Background:** The mitochondrial genome (mtDNA) is a 37-gene, circular, 16.5 kb genome. Mitochondrial dysfunction caused by pathogenic/likely pathogenic variants in the mtDNA has been associated with retinal disease and vision loss. **Aim:** To assess mtDNA variants in a cohort of patients affected by inherited retinal disease (IRD). **Methods:** A customized, highly sensitive, mtDNA assay was developed, based on hybridization-based capture of mtDNA and next-generation sequencing (NGS), to detect very low heteroplasmy levels of SNVs, INDELS, and deletions. The mtDNA assay was validated and included in the diagnostic sequencing of 2597 IRD patients. **Results:** The mean read depth for mtDNA was 18,224x and 100% of base pairs were covered with a sequencing depth of >1000x. Sensitivity to detect SNVs and INDELS with over 10% heteroplasmy was 100%. For SNVs with 5–10% and <5% heteroplasmy, the sensitivity was 93.3% and 88.9%, respectively. A pathogenic/likely pathogenic mtDNA variant was identified in 22 patients (0.85%), including one heteroplasmic large deletion (7542bp), 5 homoplasmic, and 16 heteroplasmic SNVs. Homoplasmic variants were associated mostly with Leber hereditary optic neuropathy (LHON). Diagnostic variants were identified in eight mtDNA genes; *MT-ND1*, *MT-ND4*, *MT-ND6*, *MT-ATP6*, *MT-TN*, *MT-TH*, *MT-TL1*, and *MT-TV*. The most common variant was *MT-TL1* M.3243A>G, identified in 11 patients with retinal disease described as macular/code dystrophy. Additionally, mtDNA VUS was reported in seven cases. **Conclusion:** Adding mtDNA analysis to routine genetic diagnostic testing for IRD patients can increase diagnostic yield by >0.85%. Analysis of the full mtDNA allows the identification of several variants associated with both syndromic and nonsyndromic IRD.

### METABOLIC AND DIET DISEASE MANAGEMENT

#### The Relationship Between $\beta$ -Ureidopropionase Deficiency Due to UPB1 Variants and Human Phenotypes is Uncertain

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**Background:**  $\beta$ -ureidopropionase deficiency, caused by variants in UPB1, has been reported in association with varied

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  $\beta$ -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.

### MOLECULAR GENETICS

#### Increased Evidence Implicates *Notch3* Cysteine-Sparing Variants as a Cause of CADASIL

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**Introduction:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the leading heritable cause of stroke and vascular dementia in adults. CADASIL is a monogenic small vessel disease (SVD) caused by missense mutations in the *NOTCH3* gene. Typical CADASIL-causing mutations result in odd number of cysteine residue within the EGF-like repeats. Recurrent strokes, migraine or migraine-like headaches, progressive dementia, and pseudobulbar paralysis are the common clinical presentations of CADASIL. Atypical CADASIL variants (Cysteine-sparing) have been described in some CADASIL cases. **Aim:** A comprehensive genetic analysis of the cysteine sparing *NOTCH3* variants in patients with clinical suspicion of CADASIL. **Method:** Genetic analysis of *NOTCH3* gene, using the targeted next-generation sequencing gene panel, was performed in a large cohort ( $n = 674$ ) referred for molecular CADASIL testing from Australia and New Zealand. **Results:** One nonsense and 41 different cysteine-sparing missense variants in 115 cases (17%) have been identified. Of these variants, 10 have not previously been reported in any available databases. Twenty-one missense variants predicted to be disease causing by at least 3 of 4 *in silico* prediction tools used in this study. In addition, 32/115 (28%) cases have  $\geq 2$  compound heterozygous variants in *NOTCH3*. **Conclusion:** Our findings support the view that cysteine-sparing variants might cause CADASIL with a phenotype overlapping with/similar to that from typical cysteine altering mutations.

## The Clingen Kidney Disease Clinical Domain Working Group: Defining Solutions to the Challenge of Nephropathy Ontology and Nomenclature

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Kidney disease affects 1 in 10 people with 10% of affected individuals having a monogenic form. The ClinGen Kidney Disease Clinical Domain Working Group (CDWG) was established in 2019 with the goal of creating a comprehensive, standardized knowledge base defining the clinical validity of gene-disease relationships and expert classifications of variant pathogenicity across the full spectrum of nephropathies. The most significant challenge however, to curating the clinical genome associated with kidney disease lies in defining the disease entity. For many nephropathies, current disease nomenclature (e.g., OMIM) and ontology (e.g., MonDO) systems do not accurately reflect the underlying biology of a given disorder and are not aligned with contemporary knowledge of disease pathogenesis. Inaccuracies in disease naming have been found to mainly arise from multiple, similar disorders being considered separate disease entities rather than a phenotypic spectrum of a single disorder, and can also result from historical misidentifications and naming based on phenotypic rather than etiologic factors. The ClinGen Kidney Disease CDWG, in coordination with the ClinGen Disease Naming Working Group, are currently defining consensus recommendations for kidney disease naming, with input from representatives across the global renal community, including clinicians, scientists, and patients. Naming will follow the general, stepwise system of 'core disease name, distinguishing subtype, gene name' allowing delineation of disease entities in an informative and biologically valid manner. Implementing these changes across the multiple related, but not interdependent, ontology, and nomenclature systems will likely be a challenging undertaking, but one that will have immense benefits in clinical practice.

### A 127kb Truncating Deletion of *PGRMC1* is a Novel Cause of X-Linked Isolated Pediatric Cataracts

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**Background:** Pediatric cataracts (PC) are a rare heterogenous disease causing visual impairment in children. **Aim:** To identify the disease-causing variant in a family with apparent X-linked PC. **Methods:** Parametric linkage analysis, using Illumina OmniExpress SNP array data, was

performed using Merlin. Complete Genomics™ whole-genome sequence was used to identify variants within the identified linkage regions. Rare, segregating variants were further investigated in vivo. **Results:** The phenotype showed linkage to a 6.8Mb region at Xq24 (LOD = 2.53) and two additional regions at 1q42.2-1q43 and 3q26.31-3q26.32 (LOD = 2.44). A 127kb deletion at Xq24 was identified, which truncates the *PGRMC1* gene following exon 1. An *ERO1B* c.662C>T p.(Ala221Val) variant on chr1 segregates, but was not determined to be disease-causing with an unlikely pattern of inheritance and poor in silico predictions. Additional reports were identified of two unrelated males with *PGRMC1*-disrupting deletions and nonsyndromic intellectual disability with congenital cataracts. Knockdown of *PGRMC1* in zebrafish (*D. rerio*) lead to cataract in early development ( $p \leq .001$  compared to control morpholino), with the use of this translation blocking morpholino antisense oligo replicating full gene loss. *PGRMC1* loss is hypothesized to be causing cataract through disrupted cholesterol biosynthesis. Replication and mechanistic investigation with CRISPR knockout fish are currently underway. **Conclusion:** A truncating deletion of *PGRMC1* is the cause of the X-linked PC in this family and is a novel cause of cataracts. The identification of novel genes will expand clinical gene panels and improve diagnostic rates for this disease.

### A Novel *ATP1A2* Mutation in a Patient with FHM Type2

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**Background:** Familial hemiplegic migraine (FHM) is a severe subtype of migraine with aura with an autosomal dominant pattern of inheritance. Mutations in the *ATP1A2*, *CACNA2A*, *SCN1A* genes have been implicated in the FHM patients, causing FHM1, FHM2, and FHM, respectively. The *ATP1A2* gene plays a crucial role in maintaining the electrochemical gradients of sodium and potassium ions across the plasma membrane. **Aim:** We report a novel *ATP1A2* mutation in a patient with the phenotypes resembling that of previously reported cases of FHM type 2. A 30-year-old Caucasian female presented with episodes of typical hemiplegic migraine since the age of 10. Symptoms of attacks included right hand side weakness and numbness spreading from toes to the top of the head, dysphasia, photophobia, and mild phonophobia. She also developed severe throbbing headache (1-2 hours), nausea, and vomiting. Coma was also reported which lasted from 4 hours to 3 days. **Methods:** All the three known FHM genes were screened using the Targeted Next Generation sequencing panel (TGP). **Results:** A novel heterozygous missense variant was identified in the *ATP1A2* gene in exon 15, NM\_000702.3, c.2066G>T, p.Arg689Leu, and confirmed via Sanger method. The p. Arg689Leu was classified as likely pathogenic according to the American College of Medical Genetics (ACMG) guidelines. **Conclusion:** The novel mutation (p.Arg689Leu) expands the spectrum of mutations related to FHM2 and supports the high variability in clinical manifestation within the same family.

### Using Long-Read Sequencing to Link DNA Methylation with a Large Repeat Region *In cis* in ATR-X syndrome

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**Background:** ATR-X syndrome is a rare X-linked inherited disorder caused by a mutated *ATRX* gene and is characterized by intellectual



disability, facial abnormalities, and alpha thalassemia. Mutations in *ATRX* cause global changes in methylation patterns at CpG islands throughout the genome, including the *ATRX* target *NME4*. Understanding this phenomenon, using *NME4* as a model locus, may provide valuable information about methylation establishment during development and identify potential therapeutic targets for ATR-X syndrome. *Aim*: Develop a novel workflow to interrogate the methylation pattern of *NME4* using long-read sequencing. *Method*: The novel workflow will combine four methods. ATR-X patient DNA will be deaminated to allow 5-methylcytosines to be detected. The target region of *NME4* will be enriched using CRISPR/Cas9 targeted enrichment. The enriched regions will be sequenced using PacBio SMRT sequencing (circular consensus sequencing). The methylation pattern will be determined from sequencing data. *Results*: Preliminary results have been focussed on optimising the deamination and enrichment methodologies on control and patient DNA. The optimal conditions and ratio of magnetic beads for DNA retrieval were found and consistently achieved ~70% retrieval of input DNA in the deamination process. The primers sites for the CRISPR/Cas9 enrichment are currently being optimized. *Conclusion*: Early results are promising that the workflow can determine the methylation pattern at *NME4*. This novel method will create a tool to identify methylation patterns in regions of the genome that are inaccessible with traditional methods.

### MitoReport: Accessible Interpretation of Mitochondrial Variants

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*Background*: Testing for defects in mitochondrial DNA (mtDNA) is complicated by many factors ranging from technical to biological, making it significantly more challenging than identifying similarly pathogenic variants in nuclear DNA. In the past, this has inhibited many researchers from examining mitochondrial variants. Recently, however, available methods and resources have improved in three important respects, making mtDNA analysis significantly more tractable than previously. *Results*: We present an overview of three new important resources that significantly increase the accessibility of interpretation of mitochondrial variants. These include: the release of mitochondrial variant data in gnomAD, the publication of ACMG guidelines for interpretation of mitochondrial variants, and the availability of new tools including a standard mtDNA analysis pipeline from the Broad Institute, and our own variant curation tool we have developed called *MitoReport*. *MitoReport* integrates essential public data including population frequency, heteroplasmy levels, disease association, and specific haplogroup information into an easy to use interface, and accompanies it with predefined filters to aid in highlighting significant variants. *Conclusion*: New resources and tools significantly enhance the accessibility of mitochondrial variant interpretation, and may offer a valuable pathway to resolving causative variants in previously unsolved patients.

### A Novel Variant in Surfactant Protein A2 is the Likely Cause of Idiopathic Pulmonary Fibrosis in an Australian Family

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*Background*: Idiopathic pulmonary fibrosis (IPF) is a rare and devastating disease characterized by progressive lung scarring and functional decline, with a median survival of 2.3–6.7 years. Genetic studies demonstrate that a genetic predisposition is important in familial and sporadic IPF, though many families do not yet have a molecular diagnosis. To support further research, Australian IPF families have been recruited to our 'Genetic Research in IPF (GRIPF)' study, using the Australian IPF Registry and our network of respiratory physicians. *Aim*: To identify putative disease-causing variants in Australian IPF families. *Methods*: Genome sequencing data were generated and interrogated to identify variants that segregate with disease, are rare, and are predicted to be deleterious using in silico tools. *Results*: Preliminary analyses have identified a novel, putative disease-causing variant in a known IPF-gene (*SFTPA2*) in one of the families. The variant, c.160C>T (p.P54S), is shared by two affected brothers but absent in their unaffected mother, has a population frequency of 1/251,054 (gnomAD), and a CADD score of 23.3. The wild-type amino acid, proline, is located in the collagen-like domain of *SFTPA2*, is highly conserved, and predicted to be post-translationally modified to stabilize the protein structure. Functional assays to determine the impact of this variant are in progress. *Conclusion*: We have identified a novel, putative disease-causing variant in *SFTPA2* in an Australian IPF family. This is important for the family themselves, as variants in *SFTPA2* are linked to both IPF and lung cancer, and broadens our understanding of the molecular basis of IPF.

### AMPLIDEX® SMN1 PCR: A SCALABLE SOLUTION FOR SMA TESTING

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*Background*: Current Australasian guidelines recommend that women who are planning or in the early stages of pregnancy are offered genetic carrier screening for Fragile X syndrome, cystic fibrosis, and spinal muscular atrophy (SMA). This has led to increased demand for SMN1 exon 7 copy number testing. *Aim*: Currently, the NSW Health Pathology (NSWHP) Genomics Laboratory at Randwick provides SMA carrier screening using Multiplex Ligation-Dependent Probe Amplification (MLPA) for *SMN1* copy number determination. This assay is costly, time-consuming, and labor intensive. By comparison, the AmpliDex® PCR/CE *SMN1* Kit method is cost effective and can be automated to reduce the amount of time scientific staff spends performing benchwork. *Method*: The AmpliDex® PCR/CE *SMN1* Kit is a PCR-based assay

that relies on relative quantitation of *SMN1* exon 7 compared with an endogenous control product using capillary electrophoresis and custom AmpliEx<sup>®</sup> PCR/CE Reporter software for copy number determination. The AmpliEx<sup>®</sup> PCR/CE *SMN1* Kit method was compared to MLPA using 79 samples with known *SMN1* copy number. **Results:** Verification of the AmpliEx<sup>®</sup> *SMN1* PCR kit in our laboratory demonstrated 100% sensitivity and specificity at the clinically significant thresholds of *SMN1* copy numbers 0, 1, and 2. **Conclusion:** Implementation of the AmpliEx<sup>®</sup> *SMN1* PCR kit will allow for the upscaling of carrier screening for SMA to meet increasing demand.

### Menstrual Migraine and its Association with *HFE* SNPs (rs1799945 and rs1800562)

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**Background:** There is evidence suggesting iron homeostasis involvement in the pathophysiology of migraine. Studies have shown correlations between duration of headache and iron deposition. In addition, high migraine prevalence was recorded in women with hereditary hemochromatosis (HH). Homeostatic iron regulator (*HFE*) is the main genetic cause of HH and encodes the HFE protein, which is responsible for hepcidin activation. The two main polymorphisms known to cause HH are rs1799945 (H63D) and rs1800562 (C282Y). We hypothesized that due to *HFE* polymorphisms causing iron overload, it could also lead to oxidative stress in the brain, therefore generating inflammatory reactions that could result in menstrual migraine (MM). **Aim:** To identify whether *HFE* SNPs (rs1799945 and rs1800562) are associated with MM. **Methods:** Using a MM cohort consisting of 268 menstrual migraine cases and 142 unaffected female control, rs1799945 and rs1800562 were genotyped using Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP) assays and chi-square analysis to test for significant differences between cases and controls. **Results:** We found a significant difference between the cases and controls for the rs1799945 ( $p=0.01$ ), with the Minor Allele Frequency (MAF) higher in MM (19.5%) compared to controls (13%). The MAF in gnomAD is 14% for Non-Finnish Europeans, similar to our controls (13%). **Conclusion:** We find that *HFE* rs1799945 is significantly associated with MM, suggesting that H63D may contribute to an increased susceptibility to MM.

## NEUROGENETICS

### Research Themes in KAT6A and KAT6B Syndromes: A Scoping Review

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**Background:** Pathogenic variants in *KAT6A* and *KAT6B* genes cause syndromic neurodevelopmental disorders. *KAT6A/KAT6B* syndromes are extremely rare genetic disorders with a wide variety of signs and symptoms that vary according to the location of gene variants. Common features include intellectual disability, motor delay, speech and language deficits, feeding difficulties, and skeletal

abnormalities. As of 2020, ~300 individuals have been diagnosed with *KAT6A* syndrome and ~100 with *KAT6B* syndrome. **Aim:** A comprehensive up-to-date synthesis of the research status would aid the identification of existing research themes and assist support groups such as the *KAT6A* Foundation to achieve their mission. Our objective was to review the published evidence regarding *KAT6A* and *KAT6B* and create a comprehensive report. **Methods:** Five databases (Ovid MEDLINE, Ovid EMBASE, PubMed, Web of Science, and Scopus) were systematically searched up to 29<sup>th</sup> March 2021. To extract relevant literature, the following subject headings and keywords were combined using appropriate Boolean operators: *KAT6A*, *KAT6B*, Genitopatellar syndrome, Say-Barber-Biesecker-Young-Simpson syndrome, Lysine acetyltransferase, Histone acetyltransferase, *KAT*, *MOZ*, and *MYST3*. Our review included original, peer-reviewed articles, and conference abstracts. The selection process comprised two stages: an initial stage involving title and abstract review and second stage involving full-text review. **Results:** Our search strategy yielded 638 citations that were screened further by title and abstract. Of these, 410 articles were excluded, leaving 228 full-text articles for more detailed review. Our synthesis of these articles provides a thorough overview of current knowledge and the status of research regarding *KAT6A/KAT6B* syndromes.

### Vitamin D Receptor Mutations Influence on Course of Parkinson's Disease in Patients Treated With Levodopa

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**Background:** Parkinson's disease is the second most often occurring neurodegenerative disease after Alzheimer's disease. Vitamin D steroid hormone crucial for calcium homeostasis and bone metabolism. Several animal studies showed potential protective attributes of VD in dopamine cells. **Aim:** The aim of the study was to search for the connections between VDR gene mutations and course of PD development. **Methods:** Sequential analysis of VDR gene was performed on genomic DNA isolated from peripheral blood leukocytes of 100 patients with diagnosed Parkinson's Disease treated with Levodopa. Sanger sequencing was performed, we have also performed tandem mass spectrometry (LC-MS/MS) of Vitamin D metabolites. **Results:** From analyzed VDR gene fragments splicing region of exon 1 turned out to be the most interesting one. Mutation of 'start' (ATG) codon was detected in most cases. In examined patients, C/C genotype was present 32 times, C/T 53 times, and T/T 23 times. Patients in research group had a statistically significant prevalence of SNP. We found that dominant C/C alleles showed statistically earlier average age of diagnosis. In addition, the presence of each subsequent T allele significantly delayed the onset of the disease ( $p = .014$ ). We have also connected C/T genotype of rs2228570 variant with a higher chance of levodopa-induced dyskinesias. Detected metabolites concentrations also further underline this connection. **Conclusion:** We conclude that VDR gene mutations may influence the course of Parkinson's disease. Widely advised Vitamin D supplementation may not have an expected impact on the course of Patients with such changes.

## An Integrated Neurogenomics Clinic — 28 Months Experience and Outcome of a Tertiary Referral Centre

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**Aim:** To retrospectively review attendance and outcomes of a single center, integrated multi-disciplinary neurogenomics clinic at St Vincent's Hospital, Sydney, Australia. **Methods:** An audit of patients who attended the neurogenomics clinic was conducted over a 28-month period from 2017 to 2020. The clinic comprises neurologists, clinical geneticists, and genetic counselors assessing each of the patients concurrently during the consultation. **Results:** In the audit period, 99 new patients were referred spanning 45 different clinical diagnoses. Following clinical assessment, 23% ( $n = 23$ ) of referring diagnoses were revised. 79 patients (80%) undergoing genetic testing. The types of genetic testing ordered include 41 exome-based panels, 14 whole genome sequencing, 13 single gene tests, 30 repeat disorders, and 2 chromosomal microarrays. A diagnosis was achieved in 29 patients (29%), of which the majority ( $n = 22$ , 79%) were confirmed with molecular testing. The remainder had a clinical diagnosis where genetic testing was not undertaken. Of 79 patients who had genetic testing, 57 patients (58%) did not get a molecular confirmation of the clinical diagnosis. Following testing, 2% of patients ( $n = 2$ ) had their diagnosis revised. From referral to the results of genetic testing 25% ( $n = 25$ ) patients had their diagnosis revised. **Conclusions:** Provision of an integrated multidisciplinary neurogenomics clinic in a tertiary setting provides an invaluable service with a diagnostic yield of 30%. Such a model is a gold standard for diagnostic evaluation of patients with suspected neurogenetic diagnosis. Psychosocial benefits for patients, such as convenience/satisfaction of an MDT clinic, psychological closure for patients/families, and reproductive options enabled by achieving a genetic diagnosis, will be audited via a patient survey.

## Deciphering the Role of Altered THOC2/TREX mRNA Export in Neurodevelopmental Disorders Using a Patient-Inspired Thoc2 Mouse Model

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**Background:** We have implicated TREX-mediated mRNA export from the cell nucleus to the cytoplasm in neurodevelopmental disorders (NDDs) through the identification of pathogenic variants in the X-linked THOC2 gene. We have identified and studied >25 variants in patients with variable neurocognitive phenotypes. The mechanism of how altered THOC2/TREX function causes NDDs is not well understood. **Aim:** To generate a Thoc2 Exon 37-38 deletion mouse model, similar to a patient variant, to study the molecular, cellular, and behavioral consequences of compromised THOC2/TREX function. **Methods:** Extensive investigations on the Thoc2 Ex37-38 del mouse model generated by CRISPR/

Cas genome editing, after several attempts to introduce SNVs failed. **Results:** Thoc2 Ex 37-38 del is the first mouse model of the TREX complex. We have: (1) Confirmed absence of off-target effects due to CRISPR/Cas editing by WGS. (2) Thoc2 Ex37-38 del male mice are smaller in size and weight ( $\square$ 15%) compared to their wild-type littermates; a phenotype similar to the patient. (3) Thoc2 protein in Ex37-38 del male mice cortices is smaller than the wild-type protein. 4. Ex37-38 sequences are deleted in male Thoc2 mRNAs. We are currently undertaking behavioral, in vivo and in vitro neuronal assays along with transcriptomic and proteomic investigations to determine consequences of Ex37-38 del on neural cell development, differentiation, and function. **Conclusion:** We have generated a mouse model of THOC2/TREX complex taking advantage of a specific patient variant and phenotype, which we show is genuinely recapitulated in this mouse model paving way for detailed cellular and molecular investigations.

## Review of Literature on Genes Reported with Spinal Muscular Atrophy

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**Background:** Spinal muscular atrophy (SMA) is a heterogeneous group of disorders categorized by degeneration of anterior horn cells (AHC) in the spinal cord. SMA is the second most common autosomal recessive disorder and most commonly reported with SMN gene mutations. SMA type 1 is the most commonly reported lethal genetic cause of infant mortality. Genes reported with SMA could be classified according to clinical phenotype and molecular basis. There are various other non-SMN genes in online medical databases that lead to AHC degeneration and can be classified as non-SMN SMA. There is a paucity of literature for reviewing these genes, discussing the associated genotype and phenotype, and investigational strategy for SMN mutation-negative SMA cases. **Aim:** To review all SMN and non-SMN genes reported with SMA regarding clinical phenotype and investigational strategy. **Materials and Methods:** Single gene disorders by search with a phrase within a field (('SPINAL MUSCULAR ATROPHY')) from OMIM and PubMed are downloaded and analyzed. The authors have tried to classify all these entries on the basis of genotype and phenotype. **Results:** All genes can be clinically classified in four categories, but the functional classification of genes was not in order. **Conclusion:** Genes related to SMA are most commonly delineated with SMN genes, but non-SMN genes are also not a rare cause for SMA. Initially, cases may be asymptomatic with non-SMA genes, so those cases need to be followed up. Proper diagnosis is helpful for management and genetic counseling. The molecular approach may help to define pleiotropy.

## Influence of Genetic Variability on the Clinical Course of Parkinsons Disease and Efficacy of Levodopa Treatment

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**Background:** Parkinson's disease is the second most common neurodegenerative disorder in the world with Levodopa being the gold



therapeutic standard. The response to levodopa treatment may be varied, possible from the fact that the genetic variability may determine the response to the treatment. **Aim:** The aim of this work was to investigate the impact of genetic variants in the genes coding monoamine oxidase B (MAOB), dopamine receptor D2 (DRD2), and DOPA decarboxylase (DDC) on the observed differences in the clinical course of Parkinson's disease and the effects of levodopa treatment in the diagnosed patients. **Methods:** 126 patients: women and men aged 39–95 were included in the study. Peripheral blood samples were drawn, the genetic material in the form of DNA was extracted and the genotyping of single nucleotide polymorphisms (SNP) was performed using the TaqMan probes. **Results:** We detected rs2283265 and rs1076560 genetic variants of the DRD2 gene determining more frequent presence of dementia and higher patients' scores in the II and III part of the UPDRS ( $p < .05$ ) with results regarding the levodopa side effects did not reach statistical significance. We also demonstrate that the rs1799836 genetic variant of the MAOB gene and rs921451 of the DDC gene does not affect the clinical course of Parkinson's disease ( $p > .05$ ).

**Conclusion:** We believe that genetic sequencing may in the future serve as an tool to assess the future course of PD.

### Rett Syndrome and KAT6A-Related Disorders: Chromatinopathies With Overlapping Clinical Trajectories

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**Background:** Chromatin regulation is one of the most notable pathways affected in neurodevelopmental disorders (NDDs) including Rett syndrome (RTT), a pediatric-onset progressive neurological condition. Individuals with some but not enough diagnostic criteria are often referred to as RTT-like. Although RTT is mainly caused by pathogenic variants in the X-linked transcriptional regulator Methyl-CpG-binding protein 2 (*MECP2*) gene, up to 13% of RTT individuals are genetically undiagnosed. **Aim:** We aimed to use the combination of next-generation sequencing (NGS) in a cohort of genetically undiagnosed RTT/RTT-like individuals to better understand the genetic and clinical spectrum of RTT and related NDDs. **Methods:** Using NGS, we have identified five RTT/RTT-like individuals with pathogenic variants in *KAT6A*. We then undertook a thorough systematic re-assessment of 76 previously published individuals with *KAT6A*-related disorder (Kennedy et al., 2019), which

led to the re-classification of an additional two patients as RTT/RTT-like according to the Neul diagnostic criteria for RTT. **Results:** We report seven individuals with pathogenic variants in *KAT6A* who have overlapping clinical features with RTT and *KAT6A*-related disorders. All de novo heterozygous, late truncating variants were clustered in exon 17 of *KAT6A* and resulted in loss of the well-conserved C-terminal domain critical for binding of transcriptional co-regulators for regulation of target genes expression. **Conclusion:** Although variants in *KAT6A* have been previously associated with *KAT6A*-related disorders, the association with RTT appears to have been previously unrecognized. This is the first report linking RTT/RTT-like clinical phenotypes with pathogenic variants in *KAT6A*, expanding the overlapping landscape of NDDs.

### Clinical and Genetic Review of 263 CTNNB1 Germline Variants in Neurodevelopmental Disorders

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The *CTNNB1* gene encodes the  $\beta$ -catenin phosphoprotein that is best known for its dual roles in regulation of Wnt signaling pathway and cell-cell adhesion. Heterozygous, loss-of-function, or dominant-negative germline variants of *CTNNB1* cause neurodevelopmental disorders, while somatic gain-of-function variants are enriched in cancers. We aimed to characterize the clinical spectrum of *CTNNB1* syndrome in 41 novel and 222 additional individuals from

the literature and public clinical-genetic databases. Aggregation of clinical information revealed a relatively homogeneous syndrome encompassing motor delay (90.7%), developmental delay (90.7%), craniofacial dysmorphism (88.1%), delayed speech and language (87.1%), truncal hypotonia (84.1%), eye defects (83.5%), microcephaly (80.4%), peripheral spasticity/hypertonia (75.9%), intellectual disability (74.6%), and behavioral abnormalities (70.7%). Using Phenomizer, the combination of these 10 phenotypes differentially diagnosed Angelman syndrome (MIM: 105830), with absence of seizures a distinguishing feature of *CTNNB1* syndrome. Ninety percent (237/263) of *CTNNB1* variants we identified were loss-of-function and expression of  $\beta$ -catenin mRNA was reduced due to nonsense mediated mRNA decay in two available patient lymphoblastoid cell lines. To aid clinical interpretation of missense variants of uncertain significance (accounting for 20/263; 7.6% of the cohort), we implemented a functional genomic test based on the role of  $\beta$ -catenin in Wnt signaling (TOPFlash luciferase reporter assay). Of three missense *CTNNB1* variants selected based on patient phenotypes, two were dominant negative and significantly repressed reporter gene expression. The TOPFlash luciferase reporter assay is therefore effective for resolving the pathogenicity of some missense variants for individuals fitting our defined clinical picture of *CTNNB1* syndrome.

### Massimo's Mission: Developing Better Outcomes for Australian Patients with Leukodystrophies

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**Background:** Leukodystrophies are genetic white matter disorders that are estimated to have an incidence of 1 in 7000 live births. These conditions are often associated with an early onset, lack of treatment options, severe symptoms, and premature death. **Aim:** Massimo's Mission builds on the Australian Genomics Leukodystrophy Flagship and aims to (1) provide increased genetic diagnoses for Australian patients with leukodystrophies and (2) pilot the rapid development of cell and animal models for pre-clinical testing of candidate-targeted therapies. **Methods:** Patients are recruited through clinical services, patient groups, and online advertisements. Registry data is collected and managed using REDCap. Undiagnosed patients are provided clinical trio whole genome sequencing with a turnaround time of 15 working days. Those that remain without a diagnosis are triaged into our research program. Human-induced pluripotent stem cell (hiPSC) and rodent models of leukodystrophies are being established and comprehensively characterized. These models comprise hiPSCs and transgenic mice carrying disease-causing mutations as well as conditional knockout mice. **Results:** We have established the first patient registry for Australians with white matter disorders ( $N = 131$ ) and a monthly clinic at the Royal Children's Hospital in Melbourne. Analysis of unsolved cases is underway

( $N = 25$ ). The stem cell and mouse disease models have significantly advanced the understanding of the pathophysiology underlying leukodystrophies and have enabled therapeutic proof-of-concept studies. **Conclusion:** This research is important for improved diagnosis and treatment of leukodystrophies and will contribute natural history data to assess the efficacy of future clinical trials.

### NEWBORN SCREENING

#### Principles of Genomic Newborn Screening Programs: A Systematic Review

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**Background:** Genomic newborn screening (gNBS) may optimize health and wellbeing. Screening programs are required to be evidence-based. **Aim:** We aimed to provide a literature review to identify what is known and provide key points for the design of gNBS. **Methods:** A systematic literature review identified 36 articles that addressed: What is the interest and what would be the uptake of gNBS? What diseases and genes should be included? What is the validity and utility of gNBS? What are the ethical, legal, and social implications? Articles were only included if they generated new evidence, all opinion pieces were excluded. **Results:** There is consistently high interest and support for expanding to gNBS from surveyed populations. Key findings were the need for equitable access, education, and flexible consent. Gene-disease inclusion is contentious and varies according to the process used to prioritise conditions. The process for gene selection should be transparent and reflect that parents value certainty of a result in predicting disease over actionability. Analysis should minimise uncertainty and incidental findings. The expansion of screening needs to be balanced against the complexity of consenting parents for genomic testing and the risk that overall uptake of screening may decline. The literature reflects that the right of a child to self-determination is valued above the possibility of the whole family benefiting from gNBS. **Conclusion:** Overall, the literature supports the use of gNBS. Its inevitability therefore requires that a rigorous, evidence-based and nuanced approach is taken when designing and evaluating programs.

#### Prenatal Genomic Testing: Towards Early Pregnancy Counseling

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**Background:** Since 2018, we have performed prenatal and post-mortem fetal hydrops testing as virtual panels on an exome backbone.

In 2020, we introduced prenatal exome trios for real-time clinical decision making. *Aim:* We reviewed the outcomes of testing in 2019 and 2020. *Methods:* An audit of the number of referrals, diagnostic outcomes, and evaluation of rapid trio versus panel testing was performed. *Results:* 13 trio and 51 singleton prenatal tests were reviewed. Turn-around times were significantly faster for trios than for singletons (14 days vs. 44 days), reflecting the desired change in practise for genomic results to be available as early as possible. Diagnostic rate for fetal hydrops was 28% and 33% for trio vs virtual panels, respectively, and 14% to 27% for other fetal abnormalities. Noonan syndrome was the predominant cause for prenatal hydrops (4x *PTN11*, 3x *LZTR1*, 1x *RIT1*, 1x *SOS1*), while Costello syndrome (*HRAS*), MPS-VII (*GUSB*), and Escobar syndrome (*CHRNA3*) were other causes. Lymphatic genes were identified in 4 other pregnancies (3x *PIEZO1*, 1x *FOXC2*). Compound heterozygous, pathogenic *NEB* variants were detected in a fetus with bilateral talipes, possible short limbs and raised NT. The report was issued at 21+3 weeks gestation. In a pregnancy with fetal cardiac anomalies and AVSD no genetic cause was identified by trio exome analysis. After birth, the baby deteriorated and cardiac surgery was considered. Rapid review of the existing exome data allowed assessment for Kabuki syndrome which was also negative. *Conclusion:* We have successfully expanded our prenatal genomic testing to offer early trio testing to assist in real-time pregnancy counseling.

### Psychosocial Benefits and Harms of Noninvasive Prenatal Screening: Clinician and Patient Perspectives

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*Background:* Noninvasive prenatal screening (NIPS) is being increasingly used by expectant parents. Much provision of this test in Australia is occurring in clinical settings where specialized genetic counseling is unavailable, such as general practice. Potential psychosocial consequences from this kind of prenatal genetic screening remain largely unexplored. *Aim:* This study aimed to investigate potential psychosocial consequences from prenatal genetic screening tests. *Methods:* We conducted a thematic analysis of semistructured qualitative interviews with 17 Australian clinicians who order, interpret, and/or discuss results of prenatal genetic tests with expectant parents, and with 13 women who received an increased-chance prenatal screening result. *Results:* While clinicians perceive NIPS to have

important benefits, most identified unintended negative consequences arising from how NIPS was offered, and how results were delivered; potentially resulting in false reassurance or increased patient anxiety, distress, and uncertainty. Most women interviewed had positive opinions of NIPS. However, some received inadequate pretest counseling which potentially contributed to negative psychosocial consequences, including increased anxiety and distress. Several women were unaware of the genetic conditions that NIPS screened for and were subsequently surprised when they received increased chance results for these conditions. Increased-chance results, both true and false positives, caused some women to feel that bonding with their fetus had been significantly disrupted while they awaited diagnostic test results. *Conclusion:* Our results indicate that there is a need for clinician training and guidelines around the interpretation of prenatal genetic tests and pre- and posttest counseling, particularly as NIPS continues to be ordered in general practice.

### Australian Application of Novel Prenatal Rasopathy Testing Guidelines

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*Background:* Testing for RASopathy during pregnancy has been ordered relatively sporadically and protocols/laboratory accreditation for this testing have been lacking. Recent literature has provided new guidelines around when prenatal RASopathy testing is most appropriate: Stuurman et al. (2019) recommend RASopathy testing in fetuses with nuchal translucency (NT)  $\geq 3.5$ mm plus another RASopathy-related ultrasound finding, and in fetuses with an isolated NT  $\geq 5.0$ mm. Implementation of these guidelines in Australasian services has not been reported. *Aim:* To apply the guidelines outlined by Stuurman et al. (2019) to an appropriate patient cohort and report on the use of these guidelines at our service. *Methods:* Eligible patients were offered prenatal RASopathy testing from June 2019 to May 2021. Prenatal RASopathy testing consisted of next generation sequencing (NGS) of 18 genes through Mater Pathology in Queensland. Indications and outcomes are reported here. *Results:* Five fetuses had RASopathy testing. The most common indication was isolated NT  $\geq 5.0$ mm. Of five tested, two fetuses had pathogenic variants (in *RIT1* and *PTPN11*), one of which also had a variant of unknown significance (in *PTPN11*). Three fetuses had no variants detected. *Conclusion:* With the growing use of NGS in pregnancy, balancing the cost, scope, and timing of investigations has led to increasingly complex testing decisions for prenatal services. Clear testing guidelines help services offer appropriate and timely testing and enable discussions around all relevant genetic investigations early in the patient's journey. Women will benefit by having a pathway of investigations to come, should they wish to proceed.