

## Abstracts

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

## Posters

### P1. Rapid mRNA Splicing Analysis Confirming Pathogenicity of a Novel Homozygous ASNS Variant in a Newborn

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**Introduction:** Rapid genomic diagnosis programs are revolutionizing pediatric and neonatal intensive care. Determining pathogenicity of variants of uncertain significance within clinically relevant timeframes remains challenging. We describe rapid mRNA splicing analysis of a variant of uncertain significance detected by rapid exome sequencing (rES). **Case:** A male newborn ventilated for apnoea with microcephaly and cerebellar hypoplasia, whose sibling died in similar circumstances, underwent rES, identifying a novel homozygous ASNS splicing variant of uncertain significance in 75.5 h (Chr7(GRCh37):g.97482371C>T; NM\_133436.3(ASNS):c.1476+1G>A). **Methods:** ASNS splicing was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR) and Sanger sequencing of mRNA from whole blood collected from the proband and parents, and cryopreserved fibroblasts from the deceased sibling, with simultaneous Sanger sequencing-based segregation of the variant in the deceased sibling. Hospitalization costs were estimated based on average daily NICU costs and compared to the deceased sibling. **Results:** mRNA splicing analysis in the proband and deceased sibling, also homozygous for the variant, confirmed abnormal ASNS splicing with no residual normal splicing. The variant was reclassified as pathogenic at age 27 days, diagnosing asparagine synthetase deficiency (MIM 615574). Intensive care was redirected towards palliation. Time from initial rES report to variant reclassification was 22 days. Based on the difference in length of stay, early diagnosis reduced hospitalization costs by \$85,500. **Conclusions:** Rapid mRNA splicing analysis allowed prompt variant reclassification, redirecting intensive care within a clinically relevant timeframe. This case highlights the benefits of integrating studies to determine pathogenicity of variants of uncertain significance into rapid genomic diagnosis programs.

### P2. pRapid Mitochondrial Genome (mtDNA) Sequencing: Facilitating Rapid Diagnosis of Mitochondrial Diseases in Pediatric Acute Care

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**Introduction:** Standard rapid genomic testing techniques analyze nuclear DNA variants using exome and/or genome sequencing (ES/GS). Rapid mtDNA analysis is not routinely available, particularly in centres performing ES, which does not deliver clinical-grade mtDNA sequencing. We describe our experience using rapid mtDNA sequencing in tandem with an ES-based rapid genomic diagnosis program as part of the Australian Genomics Acute Care flagship. **Methods:** Two infants presenting with persistent lactic acidosis and bone marrow failure were recruited for rapid genomic testing. With clinical suspicion of mitochondrial disease, both infants underwent rapid ES and mtDNA sequencing in tandem, the latter using Nextera libraries from a full length mtDNA amplicon. **Results:** ES was non-diagnostic in both infants. mtDNA sequencing identified a single large mtDNA deletion in both infants, diagnostic of Pearson syndrome (MIM 557000). Diagnostic reports were issued within 73 h 55 min and 54 h 25 min, respectively. Both infants avoided invasive bone marrow biopsies and a range of other investigations. **Conclusions:** Rapid mtDNA sequencing in tandem with ES results in additional diagnoses in seriously ill children with suspected mitochondrial pathology, suggesting that ES alone may be insufficient in this setting. When designing rapid genomic diagnosis programs, centres should consider incorporating mtDNA amplification and analysis in individuals with suspected mitochondrial pathology, by combining ES and mtDNA sequencing in tandem, or analysing mtDNA data from GS, which captures the mitochondrial genome.

### P3. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) Caused by a Homozygous Intragenic AIRE Deletion Detected by Chromosomal Microarray

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**Background:** A common indication for genomic sequencing is suspicion of an autosomal recessive condition in consanguineous families. Detection of deletions, including homozygous deletions, beyond the current technical limits for genomic sequencing requires other diagnostic methods, including cytogenetic analysis. **Case report:** A 15-year-old male with consanguineous parents presented with congenital hypoparathyroidism complicated by hypocalcemia, cataracts, and nephrocalcinosis; oesophageal candidiasis; abnormal nails; and autoimmune/autoinflammatory hepatitis. Exome sequencing performed prior to his relocation to Australia was non-diagnostic. His clinical presentation was thought to be consistent with but not diagnostic for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (MIM 240300), an autosomal recessive condition caused by biallelic AIRE variants. **Methods:** Chromosomal microarray was performed on blood on the Illumina Infinium GSA-24 v1.0 platform with a resolution of 0.20 Mb. Interpretation was based on assembly hg19/GRCh37 (Feb 2009). **Results:** A homozygous interstitial 0.54 kb null deletion involving exons 2–3 of AIRE was identified within a region of homozygosity in the chromosomal region 21q22.3. Segregation of this deletion in four siblings identified a homozygous deletion in one younger sibling previously thought to be clinically unaffected, and a heterozygous deletion in two siblings indicating carrier status. **Discussion:** Homozygous deletions are an uncommon cause of autosomal recessive conditions in consanguineous and non-consanguineous families. To our knowledge, this is the first report of a pathogenic homozygous intragenic AIRE deletion causing APECED. In the era of genomic sequencing, and in the context of consanguinity, it is important to remember the contribution of chromosome microarray to detect pathogenic copy number changes including intragenic deletions.

### P4. Childhood Hearing Australasian Medical Professionals (CHAMP) Network: Consensus Guidelines Recommendations on Etiological Investigation and Clinical Medical Management of Childhood Hearing Loss in Australia

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Permanent hearing loss affects 1–3 per 1000 children in Australia. Universal hearing screening of neonates has facilitated early

diagnosis and access to hearing devices and early intervention services. Despite this clinical management and investigation of newly diagnosed infants is highly variable. The aim is to provide consensus recommendations for the investigation and clinical management of children with hearing loss for geneticists, pediatricians, otolaryngologists and general practitioners. The Childhood Hearing Australasian Medical Professionals (CHAMP) network was established in 2016 to improve care for hearing-impaired children in Australasia. A working group of 15 members held round-table discussions, examined existing guidelines and completed literature reviews to create a set of recommendations. Members voted on the grade and strength of recommendations using NHMRC guidelines. Recommendations are presented in three tiers: (1) First line investigations for non-syndromic hearing loss, (2) Additional investigations based on clinical presentation, and (3) Investigations to consider if tier 1 and 2 investigations are negative. In addition to detailed history taking and examination, all children with congenital hearing loss should have CMV testing, brain MRI, ophthalmology assessment and family audiograms. Children with bilateral SNHL should be offered genetic testing after adequate genetic counseling, with connexin/GJB2 testing as first-line and chromosome microarray as second-line. Where available, genomic testing (exome or deafness panel) should be considered in children with bilateral SNHL, and may reduce the need for other investigations. The role of genetic testing in unilateral loss is limited and should be guided by clinical presentation.

### P5. Clinical Report: One Year of High Dose Treatment of Proteus Syndrome with Miransertib (ARQ 092)

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A 20-year-old man with Proteus syndrome (PS) and a somatic variant in AKT1, c.49G>A (p.E17K), had thoracolumbar kyphoscoliosis, knee deformity, finger and toe macrodactyly requiring toe amputation; testicular cystadenoma; right frontal and facial bone asymmetric overgrowths starting to occlude binocular vision, asymmetric retroperitoneal lipoid overgrowth compressing the IVC, and apparent intellectual disability. Miransertib is an oral, allosteric, selective pan-AKT inhibitor that initially demonstrated activity in adults with different types of cancer with PIK3CA/AKT genetic aberrations. It was well-tolerated in pilot studies with PIK3CA-related overgrowth and PS. After baseline blood tests and total body MRI the NSW Guardianship Board approved unblinded use of 10 mg oral miransertib daily in March 2018. SL experienced only mild oral dryness. Regular hematological, biochemical, and endocrine tests were normal. Based on reports of regression of metastatic ovarian tumor and improvement in connective tissue overgrowths of a 16-year old girl with PS on 100 mg miransertib daily, SL's dose was raised to 50 mg daily (~25 mg/m<sup>2</sup>/day) which has been tolerated well since July 2018. There was one episode of gingivostomatitis attributed to herpes simplex infection, and loose painful dentition due to pre-existing periodontal disease. After 11 months of treatment, the family reported improved general wellbeing; mobility of ankles, spine and small joints of the hands; and decrease in size of the right frontonasal lesion. Width of some photographed cerebriform cutaneous

malformations on the sole had reduced by up to 10%. After 12 months' treatment, total body MRI findings were stable without disease progression.

### P6. Evaluation of a Clinical Genomics Course: Considerations for Australia and Internationally

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Genomics education lags behind the technology and research upon which it is based. As a result, there is an increased requirement for diagnostic genomic analysis training for trainees, and medical professionals from a pediatric, clinical genetic and molecular pathology background as well as scientific laboratory personnel. Here we describe the current educational landscape for genomics education available in Australia and New Zealand and review the implementation of, and feedback received from a national and international genomic analysis training course delivered in Sydney and Hong Kong. Post-course evaluation showed an improvement in confidence and knowledge in genomic testing, analyses and reporting procedures for scientific and clinical attendees. Although the responses received on both occasions were resoundingly positive, we encouraged feedback to enable genomic courses to be further refined and to address essential genomic learning requirements throughout Australia and New Zealand, and internationally.

### P7. The Changing Face of Clinical Genetics Service Delivery in the Era of Genomics

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*Purpose:* Clinical genetics is an evolving speciality impacted by the availability of increasingly sophisticated investigational technologies. Methods for monitoring the changes in workload and workflow are necessary to ensure adequate service resourcing. *Methods:* A literature search of known workload and workflow studies was completed, identifying metrics of value. A framework of metrics to allow consistent capture in clinical genetics practice was developed. This framework was then applied to local general genetics service data to evaluate recent changes in service delivery. *Results:* Literature regarding service delivery metrics in clinical genetics services is limited and inconsistent in application. The metric framework generated is a useful tool for consistent and ongoing evaluation of general genetics services. Through application of the framework new service delivery trends and significant changes in workload were identified. *Conclusion:* Studies of clinical genetics service delivery suffer from the use of inconsistent metrics. This framework will allow for monitoring of changes to service delivery, caseload volume, caseload complexity and workforce over time. Local data presented demonstrates the significant effect that implementing clinical genomic sequencing has had on clinical service delivery. Applying this framework produces a comprehensive

service characterization, enabling funding bodies to justify resourcing that addresses the growing demand of clinical genetics.

### P8. Rapid Exome Sequencing of DNA from Multiple Tissues Identifies KRAS Mosaicism in Oculoectodermal Syndrome

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*Background:* Oculoectodermal syndrome (OES) is a rare congenital condition characterized by abnormalities including epibulbar dermoids and cutis aplasia. OES was recently found to be caused by somatic mosaic KRAS variants. *Aim:* To identify the genetic basis of epibulbar dermoids, cutis aplasia, cystic lung disease (CLD), and vascular abnormalities in a critically ill infant. *Methods:* Rapid exome sequencing analyzed DNA extracted from the patient's blood, skin biopsies from affected and unaffected areas, and blood from both parents. *Results:* CLD and hydrops were diagnosed antenatally. Hydrops resolved spontaneously during pregnancy. Postnatal evaluation identified bilateral epibulbar dermoids, cutis aplasia, aortic coarctation, and vascular asymmetry. Within 72 h, rapid exome sequencing identified a de novo heterozygous missense variant in KRAS in both skin samples, NM\_004985.4(KRAS):c38G>A, resulting in p.Gly13Asp. The allele frequency in abnormal skin was higher (32%, 35/73 reads) than in normal skin (14%, 14/89 reads), and the variant was absent in the patient's blood (0/93 reads), supportive of somatic mosaicism. Analysis of genes causative for interstitial lung disease, and full exome analysis did not identify any alternative cause for CLD. *Discussion:* Severe CLD and hydrops are not previously reported in OES, though RASopathies are recognized to cause hydrops. This may represent an expanded phenotypic spectrum of OES. In critically unwell neonates, when mosaic conditions are considered, appropriate samples must be obtained for testing. The causative variant is often absent from blood in mosaic conditions such as OES and Encephalocraniocutaneous lipomatosis. Essential to this diagnosis was sampling of multiple tissues and rapid turnaround time.

### P9. JARID2 Deletions May be Associated with a Clinically Recognisable Intellectual Disability Syndrome

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Fourteen patients with de novo heterozygous deletions in the 6p22-p24 region that include JARID2 have been published so far. Common features include moderate to severe intellectual disability in 13 patients (the 14th had a partial JARID2 deletion and a borderline low IQ of 74) and characteristic dysmorphism in all. All published patients to date have deletions encompassing multiple genes, making it difficult to identify a critical gene. We report a paternally inherited deletion involving JARID2 only, with the child displaying intellectual disability and similar distinctive dysmorphic features reported in children with larger deletions. The father has

a mild-moderate intellectual disability and similar features. These findings suggest that *JARID2* may be the critical gene within the 6p22–p24 region. The lack of *JARID2* deletions in healthy population databases may indicate that this gene deletion has a high penetrance. *JARID2* is a regulator of histone methyltransferase complexes, which during embryogenesis, is predominantly expressed in neurons and particularly in dorsal root ganglion cells. We propose that *JARID2* be considered a new candidate gene for syndromic intellectual disability.

### **P10. Creating a Bi-National Clinical Genetics Lecture Series: Its Successes and Challenges**

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The Australasian Association of Clinical Geneticists (AACG) has been tasked by the Royal Australian College of Physicians (RACP) to facilitate a 'systematic and coordinated approach to both delivery of physician training and the individual Training Programs'. In 2018, the RACP Advanced Training Committee in Clinical Genetics accredited 27 training sites for 45 General Genetic Trainees. This is three fewer sites for a 75% increase in trainee numbers since 2014. As Clinical Genetics is primarily a study of rare genetic disease, each accredited site will have comprehensive knowledge of common genetic disorders and expert opinion in a subset of rare genetic conditions. Trainee proficiency is oftentimes steered towards local expertise based on their training site selection, resulting in some bias in trainee experiences. Our aim is to improve the breadth of educational experience within the Clinical Genetics training program independent of the training site. In 2019, the AACG rolled out a bi-national teaching program based on the RACP curriculum. The program consists of a three year lecture series facilitated by rare disease experts across Australia and NZ. The program takes advantage of online conferencing tools for multi-site access to the lecture series. A trainee satisfaction survey was created to assess fellows' perceptions of current educational needs. We distributed a 15 question electronic survey to the 45 Australian and New Zealand-based advanced trainees undertaking training in Clinical Genetics in 2019. Responses will guide the delivery of the training program and ensure gaps in the training program are identified and resolved.

### **P11. Ultra-Rapid Genomic Sequencing in the Neonatal Intensive Care: Expanding the TK2-Phenotype and Informing Clinical Decision**

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The increasing application of genomic sequencing in clinical practice has allowed for both novel gene discovery and an evolution in our

understanding of disease spectrum of previously recognized syndromes. This is particularly true in rare syndromes, such as TK2-related mitochondrial depletion syndrome, which can present within the spectrum of infantile onset progressive encephalomyopathy through to adult onset progressive myopathy. We describe rapid genomic diagnosis in a ventilator-dependent, premature infant presenting with microcephaly, severe neonatal hypotonia, joint contractures, neuronal migration disorder and a disproportionately small hindbrain. Trio-exome sequencing identified compound heterozygous TK2 truncating variants, with time to report of 67 h. The literature describes individuals with progressive infantile encephalomyopathy are compound heterozygous for a missense variant and a truncating variant, with <10% residual enzyme function. We postulate that individuals with two truncating variants will have very little, if any, residual enzyme activity. Palliative care was provided from day 9 of life based on the infant's clinical presentation and the progressive nature of TK2-related disease. Ultra-rapid genomic sequencing has the potential to become the standard of care within the neonatal intensive care unit. Identification of an ultra-rare genetic syndrome with a unique presentation and unique gene variants challenges the clinicians' capacity to ascribe certainty to the diagnosis and prognosis. Rapid Functional analysis becomes the limiting step in the diagnostic odyssey. Our patient broadens the clinical spectrum of TK2-related disease and highlights the challenges of introducing ultra-rapid genomic sequencing to the neonatal intensive care setting.

### **P12. A Comprehensive Audit of Lynch Syndrome Genetic Testing in Queensland and Review of the Literature**

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**Background:** Lynch Syndrome (LS) is an autosomal dominant hereditary cancer syndrome caused by germline mutations in mismatch repair genes (MMR): *MLH1*, *MSH2*, *PMS2*, *MSH6* and *EPCAM*. We reviewed various aspects of genetic testing undertaken at Genetic Health Queensland (GHQ), including, diagnostic yield, whether universal screening has influenced the number of genetic tests, gene prevalence, genotype-phenotype correlations, multigene panels and discordant immunohistochemistry (IHC). **Methods:** This was a quantitative, retrospective study of all patients who had undergone genetic testing for LS between June 8, 1996 and March 21, 2019. Data were extracted from the Kintrak database and pathology databases, electronic medical records and charts were reviewed for phenotypic information, gene variants and IHC. **Results:** The diagnostic rate for sequential gene testing was: *MLH1* 24%, *PMS2* 23%, *MSH2/EPCAM* 40% and *MSH6* 38%. The diagnostic rate of multigene panel testing was 6% (5 *MSH6* and 1 *PMS2* mutations). The prevalence of colorectal cancer among a sample of 332 patients was: *MLH1* 54.2%, *PMS2* 50%: *MSH2/EPCAM* 48.2%, *MSH6* 52%. The prevalence of endometrial cancer was: *MLH1* 5.2%, *PMS2* 13.5%: *MSH2/EPCAM* 12.5%, *MSH6* 30.6%. The median age of diagnosis of first tumor was: *MSH1* 42 years, *PMS2* 54 years, *MSH2/EPCAM* 46 years, *MSH6* 53 years. Nineteen patients were identified as having discordant IHC. Five patients with *MSH6* mutations had normal IHC. **Discussion:** Gene panel testing was useful in patients with atypical IHC and was cost and time efficient. LS may be missed in patients with discordant IHC may, particularly in the absence of family history.

### P13. Siblings with Lethal Primary Pulmonary Hypoplasia and Compound Heterozygous Variants in the AARS2 Gene: Further Delineation of the Phenotypic Spectrum

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Variants in the mitochondrial alanyl-tRNA synthetase 2 gene *AARS2* (OMIM 612035) cause infantile mitochondrial cardiomyopathy or later-onset leukoencephalopathy with premature ovarian insufficiency. Primary pulmonary hypoplasia is a rare lethal anomaly of generally unknown etiology. Two siblings died short after birth with primary pulmonary hypoplasia. The first baby presented late in pregnancy with hydrops; the second sibling was closely monitored during pregnancy with no evidence of hydrops and was not diagnosed until delivery. Neither sibling had evidence of cardiomyopathy. Whole exome sequencing detected the same compound heterozygous *AARS2* variants in both siblings (c.1774C>T, p.Arg592Trp and c.647dup, p.Cys218Leufs\*6). These variants have previously been associated with infantile lethal mitochondrial cardiomyopathy. Segregation analysis in the family confirmed carrier status of the parents and an unaffected sibling. To our knowledge, this is the first report of primary pulmonary hypoplasia with or without hydrops in the absence of cardiomyopathy associated with recessive *AARS2* variants. This further expands the phenotypic spectrum associated with *AARS2* mutations. Aminoacyl-tRNA synthetases disorders, particularly but not limited to *AARS2* should be considered with presentations of rare isolated pulmonary hypoplasia and unexplained fetal hydrops. This has important implications for genetic investigations and parental counseling.

### P14. Widening Access to Genomic Testing, A Physician Survey from the West of England

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The NHS Genomic Medicine Service is being developed to increase patient access to genomic testing. A wider range of clinicians will be able to utilize genomic testing. Education and training are needed to ensure safe and effective use. An anonymous survey of specialist doctors in the West of England Genomic Medicine Centre (WEGMC) region was devised to explore confidence, educational priorities and attitudes toward genomic testing. A shorter companion survey was distributed to clinical genetics staff. Newly constructed multiple choice, five-point Likert scale and open questions were reviewed by mainstreaming specialists and piloted by clinicians. Surveys were distributed via email to physicians who had previously requested testing through Bristol Genetics Laboratory and more widely to hospital-based doctors in the WEGMC region. Data was collected using SurveyMonkey and open

responses were qualitatively analyzed by three independent researchers to identify themes. 63 and 38 completed responses were received for the non-genetic doctor and clinical genetics surveys respectively. There was a potential over representation of physicians with greater interest and experience in genomic testing. 70% of non-genetic doctor respondents had previously ordered a genomic test and described low levels of confidence. Barriers to the integration of genomic testing into mainstream practice commonly identified included limited knowledge and training, time required to counsel patients and keep up skills in genomic medicine. Supportive strategies deemed most useful included guidelines, clarity in reporting of genomic results and clinical genetics support. Other countries planning to widen access to genomic testing may benefit from the experience in the UK.

### P15. Smith-Lemli-Opitz Syndrome – Atypical Phenotype

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In cholesterol biosynthesis, 7-dehydrocholesterol is converted to cholesterol by the enzyme 3 $\beta$ -hydroxysterol D7-reductase (sterol delta-7-reductase), which is encoded by the gene *DHCR7*. *DHCR7* is also required to reduce 7-dehydrodesmosterol to desmosterol. An elevated 7-DHC is indicative of Smith-Lemli-Opitz syndrome (SLOS) a disorder caused by pathogenic variants in *DHCR7*. Characteristically SLOS is usually associated with congenital anomalies, dysmorphisms and moderate to severe neurodevelopmental delay. Frequently observed additional findings include: microcephaly, micrognathia, cleft palate, cardiac defects, abnormal external genitalia, post-axial polydactyly, and 2–3 toe syndactyly. However, there are rare descriptions of individuals with milder phenotypes (PMID: 30925529; 31005410). We report, a male proband born with submucous cleft palate and imperforate anus. At one year of age the 7-DHC was normal. At 4 years he has mild speech delay and short stature. The parents had previously terminated a pregnancy affected with anencephaly and a subsequent pregnancy with holoprosencephaly. Trio whole exome sequencing of this fetus identified compound heterozygous pathogenic variants in the *DHCR7* gene. Our proband was found to have the same compound heterozygous variants in the *DHCR7* gene as the fetus. Repeat 7-DHC levels performed on the proband, at 4 years, was elevated in keeping with SLOS. This case highlights: (1) The wide phenotypic spectrum of SLOS even within a family, which is unusual for an autosomal recessive condition. (2) SLOS may be associated in rare cases with mild neurodevelopmental disability. (3) Exclusion of a metabolic diagnosis because of a negative biochemical marker is not absolute and if clinical suspicion remains, genomic sequencing is warranted.

### P16. Game of Genomes: The Exomes Are Coming ... What Do Pediatricians Need to Know?

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**Background:** Genomic sequencing technologies have moved from research into clinical practice, with dramatic benefits for diagnostic

yield. It follows that genomic testing will soon become standard practice for non-genetic specialists who may not have received training in genetics or genomics. A challenge will be to ensure that the correct genomic tests are ordered and result in optimal, cost-effective care. *Aim:* To explore non-genetic pediatric specialists' attitudes to and practice in using genomic tests, by analysing existing interview and survey data. *Methods:* We undertook a literature review and meta-analysis of existing interview and survey data on genetic and genomic testing by non-genetic pediatric specialists to determine current testing practice, and what further education was required to upskill in genomic testing. We then developed resources to upskill non-genetic pediatric specialists in the use of genomic tests. *Results:* 59 pediatricians, spanning 22 specialties, at one tertiary pediatric centre completed surveys and an additional 4 were interviewed. Domains explored included frequency and awareness of genetic test ordering, consent process, confidence in interpreting results and preference for education modalities. Themes identified included the heterogeneous needs of clinicians, variable consent practices, and a desire for further professional development with preference for departmental meetings and on-line learning. *Conclusion:* Education, guidelines and supports are needed for non-genetic specialists to order and interpret genomic tests to assist in the delivery of appropriate, safe, cost-effective and optimal care in clinical genomics. Findings of the literature review and meta-analysis are informing development of the decision aid, which will be presented.

### P17. Additional Acronyms for Genetics

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This poster is the final in a series of posters previously presented at HGSA on acronyms for Clinical Genetics. Clinical Genetics covers a vast number of conditions and a trainee needs to be able discuss these conditions intelligently and consider them as part of a differential diagnosis, despite never having seen the condition. This poster takes the total number of acronyms to one hundred, many of these conditions required learning in the FRACP clinical genetics syllabus and outlined in Oxford Desk Reference Clinical Genetics and Genomics. Care must be taken when developing acronyms in genetics, LEOPARD syndrome was renamed 'Noonan Syndrome with Multiple Lentigines' due to the obvious implication that the lentigines resemble the spots of a leopard. Similarly, parents' groups objected to the name CATCH-22 for 22q11.2 deletion syndrome. Indeed, one new acronyms proposed is DIGEORGE Syndrome (Deafness; Interrupted aortic arch; GH deficiency; Early learning difficulties; Obliterated thymus; Roof of mouth, Renal issues; Gastrointestinal abnormalities; Endocrinopathy (hypocalcemia, hypoparathyroidism); Schizophrenia Seizures) to replace CATCH-22. Acronyms can be a good way to learn a large of amount of information for some people, but should not be made mandatory. We continue to use the following rules for developing acronyms (1) avoid pejoratives, (2) common conditions (3) use the eponymous name if possible (4) avoid 'ABCE...' etc. and (5) include scoring systems if possible. Some new acronyms include: CHARCOT, DUTCH Lipid, EDWARD, FRIEDREICH, GLAUCOMA, GORLIN, von HIPPEL Lindau, NAIL Patella, SWACHMAN-diamond, TUBEROUS sclerosis, XERODERMA, among others.

### P18. Rapid Neonatal Diagnosis of Biallelic SPTB Mutation Causing Severe Hemolytic Anemia with Liver Failure

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*Introduction:* Erythrocyte membrane defects are an important cause of neonatal non-immune hemolytic anemia. Heterozygous mutations in SPTB, encoding  $\beta$ -spectrin, cause autosomal dominant hereditary spherocytosis. A small number of individuals with biallelic mutations have been reported, with severe consequences including hydrops fetalis and fatal or near-fatal anemia. *Aim:* We describe rapid genomic diagnosis of a novel homozygous SPTB mutation in a case of severe congenital transfusion-dependent hemolytic anemia, conjugated hyperbilirubinemia and hepatosplenomegaly, highlighting the utility of rapid genomic testing in facilitating early diagnosis and informing management in critically-ill patients. *Methods:* Clinical rapid trio exome testing was performed on DNA extracted from peripheral blood using Agilent Sureselect QXT CREv1 kit, followed by sequencing on Illumina NextSeq500. *Results:* We identified a novel homozygous missense variant NM\_001024858.3(SPTB):c.6119C>T (p.Thr2040Ile), located in the spectrin repeat region. Parents were both heterozygous for this variant. The time from sample receipt to result was 68 h. Pretransfusion eosin-5-maleimide (E5M) staining in the proband was markedly reduced (ratio < 0.6) and blood film showed marked spherocytosis including microspherocytes and nucleated erythrocytes. Both parents demonstrated mildly reduced E5M staining, with occasional spherocytes and elliptocytes seen in the maternal and paternal blood films respectively. The infant has life-threatening hemolytic anemia with progressive liver failure, and early genetic diagnosis has facilitated hypertransfusion to suppress ineffective erythropoiesis and reverse hepatic dysfunction. *Conclusions:* This case of severe prenatal hemolytic anemia due to a homozygous SPTB mutation broadens the genotypic and phenotypic spectrum of spectrin deficiency and highlights the value of rapid early genomic diagnosis.

### P19. ROSAH Syndrome: An Autosomal Dominant Ocular and Multisystem Disorder with Causative Variant, ALPK1 p.Thr237Met

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*Background:* We ascertained a three-generation autosomal dominant family with features of Retinal dystrophy, Optic nerve edema, Splenomegaly, Anhidrosis and Headaches, and named the condition ROSAH syndrome, with the identification of four other similarly affected families. Independent genome and exome sequencing,

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

## P20. Genetic Analysis of Polymicrogyria in Cohort of 124 Patients Using a Deep Sequencing Gene Panel

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**Background:** Polymicrogyria is a malformation of cortical development characterized by overfolding and abnormal lamination of the cerebral cortex. Manifestations include epilepsy, speech disturbance and motor and cognitive disability. Causes include acquired prenatal insults and inherited and de novo genetic variants. The proportion of patients with polymicrogyria and a causative germline or mosaic variant is not known. **Aim:** To identify the genetic causes of polymicrogyria in a heterogeneous cohort of patients. **Methods:** Patients with polymicrogyria were recruited from two research centers in Australia and Belgium. Patients with evidence of congenital infection or causative chromosomal copy number variants were excluded. 124 patients were tested with a deep sequencing gene panel including known and candidate genes for brain malformations. Causative variants were identified and correlated with phenotypic features. **Results:** A causative variant was identified in 25/124 (20.2%) patients. 4/25 variants were mosaic and the lowest allele fraction was 9%. The most commonly implicated genes were *TUBA1A* and *PIK3R2*. Mutations were also identified in *PIK3CA*, *NEDD4L*, *COL4A1*, *COL4A2*, *GPSM2*, *WDR62*, *TUBB3* and *TUBB2B*. A genetic cause was more likely to be identified in the presence of macrocephaly or imaging findings suggesting a tubulinopathy, such as dysmorphic basal ganglia. **Discussion:** The diagnostic yield in this cohort of patient with polymicrogyria was 20.2%. 16% of genetic causes were mosaic variants. The implications of these results for clinical assessment

and genetic testing are discussed. **Conclusions:** A gene panel test provides greater sequencing depth and sensitivity for mosaic variants but is limited to the genes included, potentially missing variants in newly-discovered genes. Clinical assessment for head size and additional brain malformations can assist in identifying patients with a likely genetic cause. The low diagnostic yield suggests polymicrogyria may be associated with genes not yet discovered, non-genetic factors or brain specific somatic mutations.

## P21. Closing a Gap for Adults with Rare and Undiagnosed Conditions: The Austin Health Adult Undiagnosed Diseases Program (AHA-UDP)

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Significant recent efforts have facilitated increased access to clinical genetics assessment and genomic sequencing for children with rare diseases, but there remains a service gap for adults. The Austin Health Adult Undiagnosed Diseases Program (AHA-UDP) is a two-year pilot project that aims to diagnose the cause of adult patients with presumed orphan Mendelian disorders. The purpose of this study is to improve the health and counseling of adults with rare and undiagnosed disorders, compare outcomes to pediatric undiagnosed diseases programs, and further strengthen local and national capacity in genomic medicine. The AHA-UDP commenced in late 2018, and early recruitment reflects the broad range of conditions seen in current Clinical Genetics practice. To date, 16 families (35 individuals) have been enrolled; phenotypic subgroups for investigation include neurology (5), syndromic intellectual disability (5), renal (2), cardiac (2), endocrine (1), and skeletal (1). The genomic analyses performed are case-specific; however, many families will have re-analysis of non-diagnostic clinical WES data followed by WGS. Preliminary results include rapid diagnosis of one multiplex family with the intronic GGCTG hexanucleotide repeat expansion in *NOP56* that underlies SCA36, which was detected in WGS using exSTRa (Tankard et al, AJHG, 2018). This study will: (1) examine outcomes from the AHA-UDP after its first year of operation, (2) compare these outcomes to that from similar cohorts of pediatric patients with undiagnosed diseases, (3) explore the utility of research-based re-analysis of clinical WES data, and (4) identify the effectiveness and benefits of an undiagnosed diseases program for adults.

## P22. Preliminary Outcomes of Breast Screening with MRI, MMG and Ultrasound in Young Women with NF1

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Young women with Neurofibromatosis type 1 (NF1) have an increased risk of developing breast cancer and poorer survival

following breast cancer diagnosis. Recent guidelines have recommended commencing breast screening between 30 and 35 years; however, the benefits and limitations of screening in this cohort are unknown and the optimal screening modality has not been established. The aim of this pilot study was to evaluate the outcomes of an ongoing annual breast screening program with breast magnetic resonance imaging (MRI), mammogram (MMG) and ultrasound (US) to: provide information regarding the diagnostic performance of MRI compared to standard mammography in young women with NF1. In this prospective single centre study, 22 women (30–47 years) with NF1 completed breast MRI, MMG and US. No cancers were identified on initial screen. 13 BI-RADS 3 lesions were identified by MRI, of these 2/13 (15%) were also detected by MMG and 9/13 (69%) by US. Eight biopsies were performed revealing 6 fibroadenoma, 1 stromal fibrosis and 1 intraductal papilloma. Follow-up MRI was recommended for 4 women. Biopsy recommendation rate at initial breast screen was 33% compared with 25% in women with BRCA1/BRCA2 mutations. Breast density was high in the majority of women (95%), reducing the sensitivity of MMG. Breast examination, by an experienced breast surgeon, did not appear to be hindered by the presence of neurofibroma. In conclusion, breast screening for young women with NF1 in a high-risk breast screening program was effective. Recruitment is ongoing and longitudinal data may inform the Australian Breast Screening Program for NF1.

### P23. Implementing Gene Curation for Hereditary Cancer Susceptibility in Australia: Achieving Consensus on Genes with Clinical Utility

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As the prevalence of genomic sequencing for hereditary cancers increases, so too does the report of new putative gene-disease relationships. However, the strength of evidence supporting the validity of these relationships varies extensively. This has sparked debate around the clinical utility of genes, with limited or contradictory evidence being included in hereditary cancer panels, leading to discrepancies across services in the genes tested for and reported back to patients. To assess consensus opinion on the gene-disease validity and clinical utility of genes for routine diagnosis of hereditary cancer in the Australian clinical setting, we distributed a survey by email to representatives from 16 public and 2 private Australian clinics offering genetic counseling and testing for familial cancer. Usual clinical practice relating to germline testing in the context of adult hereditary cancer was assessed, for a list of 157 genes, by representatives from 13 clinics. A majority was regarded as  $\geq 75\%$  agreement for or against clinical utility of the gene under evaluation. Results were presented at a face-to-face meeting to facilitate discussion of contentious genes. Through this process, we arrived at a consensus list of 44 genes

considered to have clinical utility for diagnostic testing of patients referred to Australian familial cancer clinics and highlighted a subset of genes needing publication of management protocols. Seven genes (*BARD1*, *CDK4*, *CDKN2A*, *EGFR*, *HOXB13*, *KIF1B*, *MDH2*) remained contentious after discussion and have been flagged for further investigation of the evidence for their gene-disease association and/or clinical utility in the Australian context.

### P24. Design and Implementation of Shariant: A Platform to Share Clinically Curated Variants across Australia

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The benefits of sharing genomic variant information and clinical interpretations across laboratories are well accepted, and include improved variant interpretation and patient management. Although sharing is encouraged by Australian governing bodies such as NPAAC and RCPA, Australian genetic testing laboratories do not have the resources to manually submit such data to existing databases (e.g. ClinVar), resulting in a wealth of knowledge being siloed in separate laboratories. As an Australian Genomics initiative, representatives of Australian clinical genetic testing laboratories were consulted to define key needs to enable sharing of variant classifications nationally. This has driven the development of Shariant - a controlled access platform designed to simplify sharing of curated variants for laboratories, with little disruption to their current workflow. During Phase 1, Shariant will provide: (1) automated upload to Shariant and download to commercial or custom laboratory curation software, (2) capture of detailed and structured evidence used to determine clinical significance, (3) automated notifications to alert users to clinically important classification discordances and an in-built communication platform to resolve these discordances, (4) semi-automated submission of summary information to ClinVar to share internationally (upon laboratory approval). Shariant will be rolled out to all interested Australian laboratories following completion of a pilot with three laboratories. Full technical support will be provided to assist laboratories with connection to the platform. Given the rapid growth in large-scale genetic testing in Australia, we anticipate that Shariant will be instrumental to facilitate and improve variant interpretation, and thus patient management, in the Australian setting.

### P25. Comprehensive FISH Testing to Screen for Secondary Abnormalities in Mantle Cell Lymphoma: A Retrospective Study

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**Background:** Mantle cell lymphoma (MCL) is a subtype of B-cell non-Hodgkin lymphoma (B-NHL) characterized by a reciprocal *t*(11;14) translocation and relatively poor prognosis. The translocation results in up-regulation of *CCND1* and is caused by juxtaposition of the gene to IGH in 95% of cases. Detection of *t*(11;14) by

fluorescent in situ hybridization (FISH) is widely used in diagnosis. Secondary changes such as MYC translocation and loss of TP53 can identify subgroups of patients associated with poor prognosis and aggressive disease. We therefore aimed to perform a comprehensive FISH panel to identify secondary changes in a cohort of MCL samples. **Methods:** FISH studies were performed on five *t*(11;14) positive archived MCL samples, that is, fixed cell suspensions from bone marrow or lymph node cultures. The probe panel was designed to identify abnormalities seen in other B-NHL and utilized Metasystems FISH probes to detect rearrangements of *BCL6*, *MYC*, and *BCL2*, and copy number changes of *ATM*, *TP53*, *CEP12* and *DLEU*. Two cytogeneticists analyzed 50–200 nuclei (200 where available, in accordance with NPAAC guidelines). **Results:** Overall, 14 secondary changes were observed. Gain of *BCL6* was observed in 2 cases, gain of *BCL2* in 1 case, and gain of *MYC* in 2 cases. Loss of TP53 was observed in one case, and loss of both *DLEU1* and *LAMP1* was observed in 2 cases. This study has shown that secondary cytogenetic changes are commonly identified by FISH in patients with MCL. Given the reported prognostic significance of these, expansion of FISH testing may be of value.

### P26. Prenatal Diagnosis at WRGL – Audit of Results and a Review of Testing Strategy

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The current testing rationale at Wellington Regional Genetics Laboratory (WRGL) for amniocentesis and CVS referrals includes rapid aneuploidy detection (QF-PCR) followed by a microarray or karyotype. Patients who are undergoing prenatal diagnosis for ultrasound scan abnormalities are offered microarray analysis, along with translocation carriers and families in whom a previous imbalance was detected. 10% of cases had microarray testing. Karyotype analysis is presently carried out on all other referrals. WRGL are currently reviewing lab processes in order to rationalise prenatal testing for their local NZ population. A review of the literature is being combined with a 5y audit of local referrals/results to enable evidence-based decisions regarding which tests are most appropriate for which referral groups. 1817 samples were received over the 5 year period, 26% were abnormal scan referrals and 18% had high risk MSS or NT > 3.5 mm. In total 327 abnormal results were reported, the relative incidence in different referral categories is discussed. Additionally, analysis of samples received for single gene disorders did not identify any clinically significant abnormalities not identified by QF-PCR.

### P27. The Elusive Spinal Muscular Atrophy (SMA) Diagnosis: Homozygous Sequence Variants

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One in 10,000 children are affected by SMA. Most reported cases involve a homozygous deletion or gene conversion event involving

exon 7 of the Survival Motor Neuron 1 (*SMN1*) gene (95%–98%), or a single pathogenic sequence variant and a deletion in a compound heterozygous state (2%–5%). Little is known about the frequency and associated phenotype of homozygous pathogenic sequence variants in *SMN1*. Furthermore, the detection of sequence variants in *SMN1* is complicated by the presence of *SMN2*, as these genes share 99% homology and the copy number of *SMN2* varies from 0 to 5. We present a family with two affected siblings where the proband presented in his early teens with rapidly progressive muscle weakness, wasting and areflexia. When his younger sibling presented with a similar phenotype a SNP microarray for homozygosity mapping was performed. The affected siblings share one Long Continuous Stretch of Homozygosity (LCSH) > 2 Mb which includes the *SMN1/SMN2* genes, which lead to the consideration of SMA as the diagnosis. Sanger sequencing detected a ‘homozygous’ nonsense variant, NM\_000344.3(*SMN1*):c.683T>A, in exon 5 of the *SMN1* gene. The variant is predicted to result in a premature stop codon at position 228 of the protein (NP\_000335.1(*SMN1*):p.(Leu228\*)). While segregation analysis is consistent with a homozygous variant in *SMN1*, further studies by long range PCR is still required to confirm that the variant is in *SMN1* and not *SMN2*. This family provide valuable information regarding the pathogenesis of SMA due to homozygous pathogenic sequence variants.

### P28. Virtual Gene Panel Analysis Has Diagnostic Yield Approaching That of Whole Genome Analysis

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

### P29. Screening Strategies for Recruitment and Result Reporting to Maximize Utility of whole-of-Life Genomics

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**Background:** Population genetic screening has traditionally been offered in the setting of education supported by face to-face genetic counseling and consent, followed by specimen collection. Community Genetics programs have also offered group genetics education, followed by individual consent and specimen collection. Models for result reporting can be individual or couple-based, with additional potential reflex testing for couples. Each model has advantages and disadvantages, which will vary from the perspective of the use-case (diagnostic, reproductive, pharmacogenomic, predisposition), patient, consumer, laboratory, clinician and funder. **Aim:** To determine if an optimal model exists to meet all likely use-cases and stakeholders. **Methods:** We modelled a range of recruitment and reporting strategies: (1) Pretest online or group education and counseling: Individual, couple (1-step concurrent, 2-step sequential, or reflex) [1C2SorR] or group; (2) Recruitment: Individual or couple (1C2SorR); self-selected or referral by healthcare provider (3) Analysis: Individual, or couple (1C2SorR) (4) Result reporting: Individual or couple (1C2SorR); (5) Posttest counseling: Individual, couple (1C2SorR) and pan-test. **Results:** We identified the models likely most appropriate to achieve informed consent, optimal yield, clinical utility and efficiency for the different scenarios. **Conclusion:** While sequencing costs remain high, the optimal strategy will be one where genomic data is tested once and stored in a secure repository, with periodic reanalysis generating various report types to maximize utility at minimum cost. The ideal solution appears to be 'collect and test once', followed by a lifelong mixture of education and reporting strategies as needed. This model met all scenarios.

### P30. The Molecular and Cytogenetic Diagnosis of a 46,XX SRY-Negative Male

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**Background:** A 30-year-old male presented for routine fertility screening including testing for DAZ (Deleted in Azoospermia) and conventional cytogenetic analysis with the clinical indication of azoospermia. **Aim:** To investigate a case of 46,XX Disorder of Sexual Development (DSD) using molecular and cytogenetic techniques. **Methods:** DAZ testing was undertaken using an in-house multiplex PCR followed by capillary electrophoresis (Agilent Bioanalyzer). Conventional cytogenetics (G-banding) was carried out and FISH studies were done to confirm the presence of SRY (Sex-Determining Region Y). Microarray analysis was performed to detect copy number changes using Infinium GSAv2 (Illumina) and the NxClinical program (BioDiscovery). **Results:** PCR analyses showed the deletion of all AZF (Azoospermic Factor) regions as well as the SRY gene. Cytogenetics confirmed a 46,XX karyotype and FISH verified the absence of SRY. Microarray showed 2 duplications measuring 0.65 mb and 1.78 mb involving chromosome 17q24.3. These duplications encompass the SOX9 gene and its related

regulatory regions, which have been associated with 46,XX DSD. **Discussion:** The absence of SRY is associated with a female phenotype. Upregulation of SOX9 causes Sertoli cell specification and triggers Anti-Müllerian hormone (AMH) production, causing development of the testis and regression of the Müllerian ducts. This patient is known to have genitalia consistent with a male phenotype and duplication of SOX9 and its regulatory regions could explain the 46,XX DSD diagnosis. The prevalence of 46,XX DSD is 1:20,000 of newborn males, SRY-negative cases account for approximately 10% of these, making this a rare finding.

### P31. Evolution of the VCGS CF Testing Service: Lessons Learnt

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Cystic fibrosis (CF) is a common inherited autosomal recessive condition with a prevalence of 1 in 2500 births and carrier frequency of 1 in 25. Until recently, VCGS has offered a CFTR variant panel which targeted 39 CFTR disease-causing variants. However, in 2018, up to 65% of diagnostic CF cases referred for diagnostic testing did not receive a molecular diagnosis highlighting the need to expand variant detection. VCGS recently transitioned CFTR analysis to an amplicon-based massively parallel sequencing platform that detects 179 variants for diagnostic cases, including three reduced penetrance variants. In 3 months of operation, the new assay has enabled a confirmed CF molecular diagnosis in an additional ten cases; one compound heterozygote of two previously untested variants and nine cases where a second variant that was previously untested for has been identified. While the addition of reduced penetrance variants (polyT and TG-tract variants) has increased the complexity of result interpretation as well as reporting of complex alleles and variants of variable clinical consequences, their inclusion in the panel has resulted in the diagnosis of six patients with CFTR-related disorders. This preliminary data suggests the implementation of an expanded CFTR variant assay has been successful in enabling additional diagnoses. The development of new tests to replace and improve existing tests in a high throughput, rapid turn-around-time environment has highlighted important lessons and challenges to be considered when implementing new tests in a diagnostic setting.

### P32. IDdb: A Database of Intellectual Disability Genes

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**Background:** Intellectual disability (ID) is extremely heterogeneous, both genetically and phenotypically. Examining causative variants is key to understanding this group of disorders. To address this, we have created IDdb: a database of human genes related to intellectual disability. Its purpose is to extensively characterise genes that are known to cause ID. By structuring published data and standardizing annotation, potential patterns in the underlying biology will be easier to evaluate. **Aim:** To create a comprehensive database of disease-causing ID genes to facilitate diagnostic turnaround time and

accelerate research by enabling pattern recognition of variant location, gene function, protein structure and functional pathways. *Methods:* The literature was reviewed extensively using OMIM, Orphanet and PubMed and updated monthly using ID search terms. The resulting journal articles were systematically evaluated against curation criteria and genes selected if variants reported were diagnostically robust. The genes were curated by scientists, pathologists and clinical geneticists specializing in ID. *Results:* This process has resulted in over 1900 ID genes and is the most exhaustive ID gene list to date. IDdb features include basic variant information, annotation at the transcript and protein levels, frequency, inheritance and phenotype. 3.3% were related to non-syndromic forms of ID. *Outcome:* The browsable and searchable database will be hosted on the website for the Centre for Research Excellence in Neurocognitive Disorders. *Conclusion:* IDdb has consolidated data from multiple sources, increasing the capacity for a more rapid molecular diagnosis, and provides a start point for improving the understanding of ID gene biology.

### **P33. Detecting Low Level Mosaicism in Parents of Children with Apparently De Novo Variants Using ddPCR**

Kylie Drake, Hannah Reid and Richard King

Canterbury Health Laboratories, Christchurch, New Zealand

Parental somatic and germline mosaicism is under-recognized and has a profound effect on the recurrence risk of genetic disorders. It is postulated as the origin of up to 4% of apparent de novo variants. Traditional Sanger sequencing which has been the mainstay of genetic testing to date is unable to detect mosaicism below about 20%, contributing to its under-recognition. Allele-specific single-colour digital droplet PCR (ddPCR) presents a highly customisable method for detecting and quantifying mosaicism for single nucleotide variants. ddPCR can be used to develop cost effective bespoke assays and is efficient at detecting the presence of low-level mosaicism. Using the non-specific binding properties of EvaGreen dye (Bio-Rad), wild-type and variant-specific amplicons at differing concentrations can be identified and their frequency compared, allowing the quantification of mosaicism. We will illustrate how we have used this method to detect or rule-out mosaicism in multiple families in which the proband presented with an apparent de novo variant. This technique has broad application in this intriguing and developing field.

### **P34. Customized Variant Testing: A New Zealand-Wide Variant-Specific Model for Genetic Testing**

Kylie Drake, Hannah Reid and Richard King

Canterbury Health Laboratories, Christchurch, New Zealand

The growth in whole exome and whole genome testing in diagnostic and research laboratories has resulted in the increasing use of genetic testing, and identification of an expanding list of genetic variants. Sanger confirmation of variants identified through research studies in an accredited laboratory is a pre-requisite to using these variants in clinical practice. In addition, segregation testing may provide valuable information to assist classification of an identified variant. Cascade testing of other family members provides information related to clinical and reproductive risk. Providing a cost effective, and timely service, for these aspects of genetic testing is as important as finding the causative variant. To meet this need our laboratory instigated a custom variant testing service. This service involves the custom design of primers and Sanger sequencing of any Mendelian inherited variant

identified in a family. This service was implemented to provide a rapid turn-around of results within a clinically meaningful time frame at a reasonable cost, lowering the barrier to follow up studies within at risk families. The service has grown steadily over the past two years now receiving samples from across New Zealand. We will provide a review of the service over this time – the range of testing, as well as methodologies employed.

### **P35. Whole Exome Sequencing Identifies New Candidate Mutations in CADASIL and Related Stroke and Dementia Disorders**

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*Background:* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a cerebral small vessel disease and the most common monogenic form of inherited stroke and vascular dementia. CADASIL has been historically thought to be caused by Cysteine-altering mutations in the epidermal growth factor like repeats of NOTCH3. However, increasing evidence suggests that there may be other mutations or genes causative of the disease (e.g. mutations in HTRA1 associated with CADASIL type 2; MIM# 616779). *Hypothesis:* Genetic testing for CADASIL performed at the Genomics Research Centre currently identifies mutations in NOTCH3 in ~16% of samples. This has led to the hypothesis that other genes or genetic factors likely contribute to or cause CADASIL or a CADASIL-like phenotype. *Methods:* Whole Exome Sequencing was performed using  $n = 50$  samples sent for CADASIL diagnosis. Library preparation was completed using the AmpliSeq Exome RDYTM library kits and the samples sequenced on the Ion Proton and Ion GeneStudio S5Plus systems. Analysis utilized the GRC developed VCF-DART diagnostic pipeline utilizing a 3-tiered analysis approach to identify new candidate genes and mutations. *Results:* To date, this work has identified 3 mutations associated with related small vessel disease within COL4A1 and COL4A2 genes (Tier 1); and candidate mutations in the tier 1 gene families, NOTCH3 pathway and HTRA1 network (Tiers 2 and 3). *Conclusion:* Data from this project identified new candidate mutations associated with a CADASIL phenotype and provided information that has contributed to our increased understanding of small vessel disease, related stroke and vascular dementia disorders.

### **P36. Preconception Genetic Carrier Screening in an Australian Fertility Clinic, the First 1000 Patients**

Peter Field

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Preconception screening for 1095 patients was reported using a NATA accredited Illumina Inherited Disease screening panel. 552 genes for 592 rare diseases are included. Only pathogenic/likely pathogenic variants were reported, ACMG-AMP variant interpretation guidelines were used. Thirteen carrier couples were identified with variants in the same gene (CBS\_CFTR\_DHCR7\_ERCC6\_GALT\_GJB2\_PAH\_TREX1). 637 different pathogenic/likely pathogenic variants, in 252 genes, were reported. 57% of variants were in female patients and 43% were in male patients. 101 genes

had a single variant reported. No variants were reported for 419 patients. The *CFTR* gene had 72 carriers, with 35 independent variants reported. *GJB2* had 57 carriers with 13 variants, *PAH* had 34 carriers with 15 variants, *CBS* had 31 carriers with 6 variants, *ATP7B* had 23 carriers with 17 variants and *POLG* had 22 carriers with 11 different variants. Twelve other genes had a carrier rate higher than 1 in 100. Data analysis software utilized MiSeq aligner/variant caller, Illumina Variant Studio, Alamut, ClinVar, HGMD, Google Scholar, PubMed. Nextera Flex Library preparation is currently being validated, which reduced hands-on laboratory time, improved % bases above Q30 and read depth average. Golden Helix/Sentieon, VSPipeline, VarSeq, VSCNV, VSReports and VSWarehouse enabled time savings, recording of work, interpretation/reporting any variant. A local database was created for over 1000 Australasian individuals, for SNVs, deletions, duplications, indels, splice variants and other variants for the 552 genes. Data quality continually assessed with omnomicsQ. Five NIST DNAs/no DNA controls used regularly and the laboratory participated in RCPA/EMQN NGS eQAPs.

### **P37. Development of a FRGX Methylation Test: Methylation Assessment of Fragile-X Patients by High Resolution Melting Analysis**

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Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females. The underlying cause of Fragile X is hyperexpansion of a triplet repeat leading to DNA methylation and epigenetic inactivation of the *FMR1* gene promoter. The routine diagnostic assay for Fragile X involves assessment of the triplet repeat expanded allele. However, in some cases the expanded allele does not always correlate with DNA hypermethylation where varying degrees of mosaicism and/or a non-methylated *FMR1* promoter occurs, with a mild to normal phenotype possible despite hyperexpansion. Here we show that the High Resolution Melting technique has significant scope to detect a broad range of mosaicism to within 10% accuracy. Virtually all patients were found to have DNA methylation at or near 100%. Only one patient with reduced DNA methylation (~80%) in peripheral blood DNA was identified. This patient may potentially have a less severe phenotype dependent on the level of mosaicism in neuronal cells. We will present additional patients and their associated genotype-phenotype correlation.

### **P38. Detection of an IKZF1Plus Pediatric B-ALL and the Impact on Clinical Management: A Case Study**

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We report on the diagnostic cytogenomic findings of a 7 year old female presenting with B-cell acute lymphoblastic leukemia

(B-ALL) and their impact on the clinical management. Full blood count on presentation revealed anemia and neutrophilia with the presence of circulating B-cell blasts confirmed by flow cytometry. Bone marrow aspirate morphology showed a diffuse population (75%) of lymphoblasts, which was consistent with B-lymphoblastic leukemia/lymphoma. Conventional cytogenetic testing was performed on her bone marrow using G-banded karyotype and FISH studies, which showed normal results. In addition, a routine SNP-microarray was performed, which revealed submicroscopic deletions consistent with the new B-ALL subtype IKZF1-Plus. The IKZF1-Plus subtype of B-ALL is defined by an IKZF1 deletion with one or more concurrent deletions of *CDKN2A/B*, *PAX5*, *CLRF2-P2RY8 del/fusion*, and without the presence of an ERG deletion. Patients with IKZF1 deletions have been shown to have a higher risk of relapse and those with an IKZF1-Plus genomic profile have an even higher risk of relapse irrespective of MRD response by quantitative PCR. With the implementation of SNP-microarrays, we were able to determine that this patient was in a high genomic risk category with a significantly increased risk of relapse at diagnosis. The patient has subsequently had their treatment intensified and in consolidation is stratified into the early High Risk Treatment Group.

### **P39. A Novel ATM Deletion in a 2-Year-Old Female with Variant Ataxia-Telangiectasia**

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Ataxia-telangiectasia (AT, OMIM# 208900) is a rare neurodegenerative disease classically characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. AT is an autosomal recessive condition caused by disease causing variants in the *ATM* gene, which plays an important role in the activation of cell-cycle checkpoints and initiation of DNA repair in response to DNA damage. A 2-year-old female with abnormal gait, ataxia, dystonia and persistent elevation of alpha fetoprotein but no telangiectasia was referred with suspected variant AT. The patient had no family history and the parents were non-consanguineous. Massively parallel sequencing (MPS) of the *ATM* gene identified a heterozygous pathogenic variant, c.4143dup (p.(Pro1382Serfs\*6)). No other *ATM* variants were identified despite 100% coverage of *ATM*, including the known pathogenic intronic variant (c.5763-1050A>G). Further testing was carried out to look for a second *ATM* variant. A high-density chromosome microarray identified a novel 34 kb deletion involving the last exon of *ATM* and part of the *C11orf65* gene. The deletion was classified as likely pathogenic based on the American College of Medical Genomics guidelines. Re-examination of the MPS data showed a number of reads bridging across the breakpoints. Subsequent parental testing showed the variants to be in trans, which has implications for their own risk of developing malignancies, as well as for future pregnancies. This case highlights the importance of looking for copy number variants in recessive disorders where there is a strong clinical phenotype correlation and a single pathogenic variant is identified.

#### **P40. Re-analysis of Massively Parallel Sequencing (MPS) Data for Aortopathy and Ehlers-Danlos Syndrome (EDS) Panels**

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Massively parallel sequencing (MPS) has allowed the screening of multiple genes simultaneously and has been applied to many diseases including the aortopathies: Marfan syndrome, Loeys-Dietz syndrome (LDS), familial thoracic aortic aneurysms and dissections (TAAD) and related disorders. Research has led to an increasing number of genes being associated with aortopathy disorders. In addition, there is considerable overlap between the clinical phenotypes of LDS and EDS with a clinical need to identify the vascular subtype of EDS. Our laboratory began offering an aortopathy panel, containing 17 genes, by MPS in 2014 using the Illumina TruSight One capture. To explore whether reanalysis with expanded gene lists improved the diagnostic yield, MPS data was reanalyzed for the current aortopathy (24 genes) and EDS (15 genes) panels. A subset of 74 patients, who were tested previously for the aortopathy and/or the EDS panel with no pathogenic variants identified, were included in this study. Two likely pathogenic variants, in *COL5A1* and *COL5A2*; and four variants of uncertain significance (VOUS) in *LOX*, *MED12*, *MYLK* and *ZNF469* were identified. This resulted in a yield of 2.7% (2/74) of pathogenic variants with another 5.4% (4/74) of variants with potential significance. The pathogenic variants enabled confirmation of classic type EDS in two previously undiagnosed patients. Reanalysis of existing MPS data from clinical exomes or whole exomes is beneficial. However, reanalysis does require significant resources. Currently, the process of initiating any reanalysis needs to be clinically driven and could be done at the time of clinical review.

#### **P41. Phenotypic Child with Two Supernumerary Marker Chromosome 15s Without SNRPN, UBE3A, OCA2 or HERC2 Involvement**

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**Background:** Chromosome 15q11q13 is a hot-spot for cytogenetic rearrangements such as small supernumerary marker chromosomes (sSMC). Most chromosome 15 derived sSMCs (sSMC(15)) are associated with a phenotype and characterized by identifying Prader-Willi/Angelman syndrome (PWS/AS) genes; e.g. SNRPN at 15q11.2. We present a case involving two different sSMC(15)s with unusual PWS/AS gene involvement in a 4 year old girl with moderate global delay. **Method:** 4x180K CGH+SNP microarray was performed and follow-up testing involved karyotyping, 15q11q13 methylation-specific (MS)-MLPA, and FISH using pancentromere and DZ15Z4 probes. **Results:** CGH microarray showed a complex genomic abnormality involving one duplication and three non-contiguous triplications between 15q11.1 and 15q13.1. These totalled

7.78 Mb, involved ~47 RefSeq genes [CHEK2P2 to TJP1] but not SNRPN, UBE3A, OCA2 or HERC2. Karyotyping showed mosaicism involving a ring and minute-shaped sSMC(15). MS-MLPA showed MAGEL2 hypermethylation, indicating the sSMC(15)s were maternally derived. Pancentromeric FISH showed signals for the ring and minute-sSMC(15), however only the minute-sSMC(15) showed DZ15Z4. **Discussion:** This case involves a maternally derived ring and minute-sSMC(15) with duplication and triplication of chromosome 15q11.1q13.1 material but not SNRPN to UBE3A, OCA2 or HERC2. 15q11q13 is known as the recurrent microduplication region and is associated with a phenotype when maternally derived. However, our patient's features are not as severe. Maternal methylation of the triplicated 15q11q13 locus could result in silencing MKRN3 to PWRN1 expression. 15q11.2 proximal sSMC(15)s not involving SNRPN are usually innocuous, which suggests maternally expressed genes distal to UBE3A (*ATP10A*, *GABRB3*, *GABRA5*, *GABRG3*, *APBA2*, *NSMCE3*) may be candidate genes.

#### **P42. Withdrawn**

#### **P43. A Novel Method for Gene and Region Prioritization Based on Human Phenotype Ontology (HPO) Terms**

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

#### **P44. A Duplication of 19q13.12-q13.32 in a Female Neonate with Dysmorphism and Cleft Palate**

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Chromosome 19 is the most gene-rich of the chromosomes, with high G+C content and including large clustered gene families; this

indicates high biological and evolutionary significance. Very few cases of duplications involving the long arm of chromosome 19 have been reported in the literature.

We present a new-born female patient with dysmorphic features and a cleft palate. A duplication of 19q13.12-q13.32 was initially detected by GTG-banded chromosome analysis; follow-up microarray analysis showed the duplicated region to be approximately 11.6 Mb in size and include 325 protein coding genes. A review and phenotypic comparison of published cases will be included.

#### **P45. Improving the Efficiency and Efficacy of Molecular Genetics Diagnostics for Hereditary Ataxia**

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**Background:** Hereditary episodic ataxias (EA) are a complex group of neurological disorders usually characterized by attacks of imbalance and incoordination, often associated with progressive ataxia. Weakness, dystonia and ataxia may present between episodes. Molecular genetic tests for episodic ataxia type 2 (EA2) usually target only the specific calcium channel gene (*CACNA1A*) that is known to cause EA2. **Hypothesis:** In cases where no mutations are identified in the *CACNA1A* gene, it is important to identify the causal gene so that more effective treatment can be prioritized for patients. **Methods:** In this study, patients ( $n = 16$ ) with a strongly suspected clinical diagnosis of EA2 that have previously screened negative for mutations in *CACNA1A* were analyzed using whole exome sequencing (WES) technology. **Results:** Upon sequencing the 16 EA2 samples we were able to detect a number of potential causal variants in different genes. A novel missense mutation was identified in the potassium voltage-gated channel subfamily A member 1 (*KCNA1*) gene. The *KCNA1* gene has been previously implicated in episodic ataxia type 1. In addition, three different genes were suggested to be investigated further and prioritized for functional assessment in future studies. **Conclusion:** This WES study has facilitated the identification of EA2 associated mutations in novel genes not previously implicated. The use of this technology enables greater coverage and more comprehensive analysis of implicated genes, as well as being a faster and more cost-effective method, providing substantial benefit to both clinicians and patients.

#### **P46. Benefits and Challenges of the New MBS Item Numbers for Cystic Fibrosis Gene Testing**

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Variants in the *CFTR* gene are responsible for cystic fibrosis (CF) and *CFTR*-related disorders (*CFTR*-RD). From July 1st 2018, *CFTR* gene testing was added to the Australian Government Department of Health Medicare Benefits Schedule (MBS). Six item numbers of varying rebates were introduced and are dependent on referral indication: symptoms of CF or *CFTR*-RD, prenatal or parental testing when the fetus has echogenic bowel, a close family history, a reproductive partner who is a carrier, or prenatal testing for a carrier couple. Victorian Clinical Genetics Services (VCGS) has implemented

these MBS changes aiming to streamline the claims process for our patients. The introduction of MBS for *CFTR* testing has enabled greater access to testing with no or minimum out of pocket expense for patients. We have encountered challenges regarding steps required to ascertain eligibility for these item numbers including: ensuring *CFTR* gene testing is requested by a medical specialist or consultant physician, obtaining a record of the known variant, determining the pathogenicity of variants identified from external laboratories, and Laboratory Information Management System integration. Additional laboratory and clinical resources have been required to determine whether the Medicare eligibility criteria have been met. Ongoing challenges include finding the balance between not compromising on test turn-around-time versus waiting for responses from patients and requesting practitioners, and using our resources efficiently. MBS item numbers are being introduced for genomic testing and the VCGS experience regarding these *CF* item numbers may inform other organizations on how to approach future additions to the MBS.

#### **P47. A Case Report of Familial Complex Chromosomal Rearrangement and the Essential Genetic Testing Involved**

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**Background:** Familial complex chromosomal rearrangements (CCR) involving three-way translocation in a 3-year-old male with global developmental delay was ascertained through a combination of chromosome microarray (CMA), G-band karyotype and subtelomere fluorescence in situ hybridization (FISH) testing. **Method:** CMA was performed using 'Agilent SurePrint G3' CGH+SNP Microarray 4 × 180K (Mean effective resolution: 0.13 Mb for copy number, 5 Mb for copy-neutral AOH). G-band karyotype and subtelomere FISH (6p, 6q, 17p, 17q subtelomere probes) testings were performed as per standard laboratory protocol. **Results:** CMA revealed two copy number changes: a 0.68 Mb terminal deletion within chromosome 6 band p25.3 and a 3.36 Mb terminal duplication within chromosome 17 band q25.3, which suggested a possible unbalanced translocation involving 6p and 17q [*der(6)t(6;17)(p25.3;q25.3)*]. Subsequent subtelomere FISH analysis actually revealed a CCR indicating an unbalanced three-way translocation. The 6p subtelomere signal was missing, however an additional 17q subtelomere signal was found on chromosome 15q instead of 6p. This finding was confirmed by G-band karyotype. Parental karyotype analysis disclosed that the father carries a balanced three-way translocation *t(6;17;15)(p25.3;q25.3;q24.3)* and the proband has inherited a 3:3 adjacent-1 malsegregant from his carrier father; that is, *der(6)t(6;17;15)pat* and *der(15)t(6;7;15)pat*. **Discussion/Conclusion:** A combination of CMA, subtelomere FISH and G-band karyotype testing were performed to provide a comprehensive analysis of the three-way CCR *t(6;17;15)* in this family. Such characterization is essential for the management of future pregnancies. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for the couple should be considered as chromosomally unbalanced live births can be associated with this CCR, as seen in the proband.

#### P48. Preliminary Results of an Expanded Preconception Carrier Screening Pilot Study in Western Australia

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

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

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**Background:** Expanded preconception carrier-screening has been increasingly discussed and implemented over recent years. Some have warned of limited clinical utility, while others argue that preconception carrier screening improves reproductive choices. We investigated the attitudes and knowledge of Western Australian health professionals in relation to preconception carrier screening and where their concerns lie. **Methods:** We analyzed the relationship between knowledge, attitudes and intentions to participate in preconception carrier screening using logistic regression, in 203 health professionals in Western Australia. **Results:** Almost all participants have high genetic knowledge but knowledge did not correlate with

intentions to take the test. Participants were less informed about probabilities and result interpretation than key carrier-screening concepts. Although 60.6% of participants had a positive attitude to the test, researchers and diagnostic scientists were more concerned about discrimination and confidentiality issues ( $p \leq .05$ ) while genetic counselors were worried about doing more harm than good ( $p = .04$ ). Predictors of taking the test include having a positive attitude, being a non-practitioner, not being a parent and not religious ( $p \leq .05$ ). Of the 76% of participants who would use the test, 95% indicated that they prefer to screen for both childhood lethal and chronic debilitating conditions. **Conclusions:** Preconception carrier-screening is perceived positively by WA health professionals with a high level of intention to use it if it was available. Practitioners would be effective at administering the test provided they have access to support such as a genetic counselor to clarify doubts. Pilot studies of carrier screening will address concerns identified in this study.

#### P50. To Check, or Not To Check, That Is the Question

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**Introduction:** Clinical exome sequencing has been shown to triple the diagnostic rate for one-third the cost per diagnosis compared to standard diagnostic care. It is therefore in high demand and fast becoming the 'go-to' diagnostic test for many genetic diseases. Genomic sequencing protocols involve many steps, making it inherently subject to sample mix-up, with error rates reported to be 0.1%–1%. Incorporation of sample identity tracking into clinical genomics practises to ensure result validity, especially if part of the testing process is outsourced, has been recommended. **Aims:** To determine the sample mix-up rate in a testing setting where part of the process is outsourced to a third party. **Methodology:** We performed sample identity tracking on a cohort of 536 samples that underwent exome sequencing at an external facility as part of a research project. A subset of highly polymorphic single nucleotide polymorphisms (SNPs), were chosen to determine sample identity. Genotypes from the exome data, were compared to genotypes from a MALDI-TOF Mass Spectrometry based SNP genotyping assay performed on an aliquot of the same original/stock DNA sample. **Results:** Discordant results were identified in 10 samples (1.9%). **Conclusions:** These results confirm previous investigations that sample mix-up occurs within genomic sequencing processes where part of the testing process is outsourced, at a relatively high rate. The impact of an incorrect diagnosis on patient management could be catastrophic. Sample identity tracking is therefore essential and should be standard of care for clinical genomics testing.

#### P51. The Importance of Comprehensive Workup in a Prenatal Setting

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**Background:** An amniocentesis was received from a 38 year old woman in her second trimester of pregnancy, with the clinical indication of fetal cardiac anomalies involving pulmonary valve stenosis. **Aim:** To investigate the likely cause of an abnormal phenotype in a fetus through cytogenetic and molecular techniques, and the implications of the subsequent genotype on the proband and parents. **Results:** Microarray analysis showed a male fetus with an

approximately 0.1 Mb de novo interstitial deletion of chromosome 16p13.3, encompassing four OMIM-linked disease genes, and approximately 6% LCSH across the detectable autosomal genome. The deletion encompassed the  $\alpha$ -thalassaemia implicated  $\alpha$ -globin protein genes HBA1 and HBA2. Due to clinical indication, alpha thalassaemia mutation studies by PCR were performed for the parents of the proband to determine parental carrier status for  $\alpha$ -thalassaemia mutations. Subsequent to parental mutational analysis, MLPA testing of the alpha-globin gene cluster and mutational analysis was performed on DNA extracted from cultured amniocytes. **Conclusion:** This case demonstrated the need to ensure proper scrutiny was given to every potential outcome for the fetus through appropriate follow up testing. Approaching this case from both cytogenetic and molecular genetic perspectives ensured a complete delineation could be performed to determine risk outcomes.

### **P52. Single-Colour ddPCR for the Analysis of Copy Number Variants: Rapid, Economical and Variant-Specific**

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Identifying copy number variants (CNV) is an essential part of a complete genomic examination. Currently this is most commonly performed by microarray or FISH for large CNVs, or multiplex ligation probe amplification (MLPA) for exon size deletion or duplication. Neither of these methods lend themselves to easy design of bespoke assays. We were faced with the problem of confirmation of exon size copy number variants detected by array or segregation analysis in families with identified CNVs. To overcome this we devised an easily customizable digital droplet PCR (ddPCR) assay for copy number variation. We will present a highly customisable method for quantifying CNV, using a single-colour ddPCR platform. Digital droplet PCR using EvaGreen (Bio-Rad) is a cost effective and efficient method to develop bespoke assays. We have used this method to confirm CNVs found by microarray analysis which were at, or outside, the limit of resolution. This provided a more cost effective and rapid alternative to expensive FISH probes or TaqMan assays. Specific fluorescent signals can be generated for the target and reference amplicons using the nonspecific DNA binding properties of EvaGreen dye by manipulating their concentration, enabling independent quantification. Comparison of target and reference amplicons enables effective analysis of copy number. We will present several scenarios, including mosaic deletion/duplication to demonstrate the effectiveness of this method to confirm copy number variation in patients.

### **P53. Peer Support Groups Play an Important Role in 'Social Precision Medicine'**

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The number of Peer Support Groups (PSG) that exist will continue to expand as genome sequencing advances. Their membership will grow as more people are identified with genetic diseases, and with that, their power to influence precision medicine. 'The right drug for the right patient at the right time' is the mantra of precision

medicine. PSG collectively have the power to influence genomic testing processes through a novel model called 'Social Precision Medicine'. Social Precision Medicine occurs when PSG members interact with one another to unveil commonalities within and/or between their genetic condition/s, in addition to well-documented medical symptoms that affect their members. For example, a member used a social media forum to share a photo of crayons with the paper ripped off and query if any other PSG member's child had the same compulsion. Of the 60 members in the forum, 44 responded with comments of familiarity and inclusions of other, similar compulsions. Social precision medicine can identify shared common behaviors and has the potential to contribute to a diagnosis together with phenotype and genomic testing. When symptoms appear, members can reach out to others to learn from their experiences around medications or treatment plans, both positive and negative. Members can then discuss this information with their clinicians to influence their choice of drugs and treatment options. This can prevent unnecessary trials of ineffective medicines and has the potential to save health dollars. So why aren't we analysing the impact that PSG have on precision medicine?

### **P54. Maternal Uniparental Disomy (UPD) of Chromosome 20: Presentation of Two New Cases**

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**Background:** UPD has been reported for the majority of human chromosomes with imprinted genes and UPD phenotypes well documented for chromosomes 6, 7, 11, 14, and 15. There is controversy over the significance of UPD 2, 16 and 20 with a clear phenotype often confounded by residual trisomy mosaicism. Few reports of UPD20 exist without residual trisomy. **Aim:** We describe and compare clinical features of two cases of UPD20mat to further delineate the phenotype. **Method:** We performed trio genotype analysis on two cases using the 300 K CytoSNP-12 Beadchip (Illumina) and SNP Trio bioinformatic analysis tool [<http://pevsnerlab.kennedykrieger.org>]. Clinical features of both cases were compared with other literature reports. **Results:** Case 1 showed UPD20mat (complete heterodisomy) was a 9-year-old male referred for ?RSS who presented with poor fetal growth, postnatal failure to thrive, mild feeding difficulties, plagiocephaly, facial asymmetry, torticollis and skin pigmentation. Case 2 UPD20mat [mixed isodisomy and heterodisomy] was a 4 month old male delivered early due to fetal growth concerns, which included hypotonia, poor feeding, head circumference 38 cm (2nd centile), plagiocephaly, bilateral 5th finger clinodactyly and slow growth. From four published reports of UPD20mat [14 cases] without residual trisomy, common features included growth retardation and prominent feeding difficulties, associated features included hypotonia, bilateral 5th finger clinodactyly and mild abnormalities of skin pigmentation. **Conclusion:** UPD20mat is rare and we present two new cases with clinical features consistent with previous reports. These two cases add to the

emerging evidence that defines a new imprinting disorder for maternal UPD20.

### P55. Overcoming the Bottleneck in Cancer Next-Generation Sequencing with Curation Training

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Advancements in sequencing technologies and bioinformatics allow rapid deep sequencing and variant detection. However, a significant bottleneck remains in variant interpretation for clinical reporting. To address this, Melbourne Genomics Health Alliance is committed to upskilling medical scientists and clinicians in cancer variant curation. One such strategy is a 2-day workshop introducing the processes and resources used in cancer variant curation. The workshop is most effective in a 2 part format: (A) Conceptual lectures and (B) Practical sessions including guided curation exercises and group practicals, building difficulty from simple to complex cases. To date, we have conducted three 2-day workshops, including one at the national level involving 5 states. Evaluations were conducted pre- and post- workshop to assess alterations in the participants' understanding of the topics and resources used. Of 111 participants, most were medical scientists (50%) and clinicians (25%) with 75% of all participants indicating that curation is important in their role. Post-workshop, 68% report improved understanding of the curation processes and confidence in somatic variant classification. Pre-workshop, 50% had no experience of the tools and databases used; 71% report they gained confidence using them over the 2 days. Over 90% were satisfied with the structure and content of lectures and practical sessions. The rising demand for precision medicine has led to an inevitable increase in cancer genetic testing by Australian laboratories. Refinement of the learning strategy, including tailoring to different levels of expertise, will help to meet the rising demand for curation skills in the cancer genomics workforce.

### P56. Hereditary Fructose Intolerance (HFI) Diagnosis - ALDOB Deletion Detected Using Multiplex Ligation-Dependent Probe Amplification

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**Background:** HFI is a rare autosomal recessive disease of carbohydrate metabolism causing hypoglycemia, liver and kidney failure, coma and death. The aldolase B (*ALDOB*) gene is involved with the most common pathogenic variants being *A150P*, *A175D*, and *D335K*, accounting for 64%, 16% and 5% of disease alleles respectively. Currently Sanger-sequencing *ALDOB* exons 5 and 9 identifies these variants. However, gross deletions will be missed. **Methods:** DNA from 30 patients referred to RPAH Medical Genomics laboratory between 2010 and 2019 for suspected HFI was analyzed for gross deletions using a commercial Multiplex-Ligation-Dependent Probe Amplification (MLPA) kit. This kit includes 11 probes: one for each

of nine *ALDOB* exons, and mutation-specific probes for *A150P* and *A175D*. Data were analyzed using Coffalyser software (MRC Holland) and NGRL (Manchester) spreadsheets. **Results:** A previously described pathogenic deletion of exons 2-6 was found in 1 patient with *A150P*. *A150P* and *A175D* mutations in 4 additional patients were correctly called using MLPA. **Discussion/Conclusion:** MLPA should be the preferred screening approach in HFI because it detects the 2 common missense pathogenic variants as well as gross deletions. The patient with the deletion was originally reported as being homozygous for the *A150P* mutation. However, the patient is now shown to be hemizygous. Sanger sequencing of all exons could then be undertaken in patients with clinical features strongly suggestive of HFI.

### P57. The Application of Droplet Digital PCR to Confirm an Intragenic *CDKL5* Deletion Detected by Microarray

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Microarray testing was requested for a one month old female with seizures. Analysis showed a deletion at Xp22.13, between 36 and 64 kb in size, within the X-linked cyclin-dependent kinase-like gene *CDKL5*. The apparent deletion was at the limit of the assay detection threshold (Agilent 180k CGH/SNP array), but if confirmed, was likely to be clinically significant. Deficiency of *CDKL5* causes Early Infantile Epileptic Encephalopathy, an X-linked dominantly inherited condition, characterized by early onset seizures, severely impaired motor and language skills, sleep disturbances and gastrointestinal problems. A timely diagnosis allows for implementation of early intervention therapies. A preliminary result was issued to the referring clinician pending additional testing to confirm the deletion together with parental testing. DNA samples from the child and her parents were analyzed by droplet digital PCR (ddPCR) using primers specific to NM\_001037343.1(*CDKL5*). The copy number was assessed at six sites across the gene. A de novo heterozygous deletion of *CDKL5* exon 4 was confirmed. Droplet digital PCR (ddPCR) is a relatively quick, reliable and highly cost effective method to confirm such copy number variants detected by microarray, which are close to the effective resolution of the array and below the resolution of the commercial BAC FISH probes routinely used in diagnostic cytogenomics.

### P58. Single Nucleotide Polymorphism (SNP) Microarray for Genome Ploidy and Gene Copy Number Alterations in Pediatric Acute Lymphoblastic Leukemia (PALL)

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**Background:** Identifying high-risk genetic aberrations pediatric B-cell acute lymphoblastic leukemia (pB-ALL) could allow personalized treatment intensification and improved outcomes in this patients. Recently, IKZF1-Plus deletion profile has been associated with poor outcomes; IKZF1, CDKN2A, CDKN2B, PAX5, and/or CRLF2. Along with genome ploidy [haploidy vs. hyperdiploidy] recurrent gene-fusions also remain important. In T-ALL, deletions of *STIL* result in *TAL1-STIL* gene fusion. SNP chromosome

microarray (SNP-array) is well suited to detect ploidy changes, copy number abnormalities (CNA), and copy neutral loss-of-heterozygosity (cnLOH). *Aim:* Investigate and validate an 850 K CytoSNP Beadchip array (SNP-array) for identifying ploidy, cnLOH, and CNA in pediatric ALL. *Methods:* We performed 850 K CytoSNP-array on a small cohort of pediatric ALL patients at diagnosis in conjunction with karyotype and FISH; which included B-ALL ( $n = 20$ ) and T-ALL ( $n = 4$ ). FISH was performed using probes for common gene-fusions: BCR-ABL1, ETV6-RUNX1, KMT2A-AFF1, TCF3-HLF. 850 K CytoSNP data was analyzed using BlueFuse Multi v4.5. CNA results were verified using our cancer customized CGH + SNP array and/or FISH. We categorized B-ALL patients into IKZF1wt-other, IKZF1-Plus, and absent IKZF1-Plus. *Results:* SNP-array was concordant for diploidy ( $n = 14$ ), haploidy ( $n = 1$ ), masked haploidy ( $n = 2$ ), masked hypodiploidy ( $n = 1$ ), and hyperdiploidy ( $n = 5$ ). Overall, total [ $n = 23$ ] recurrent deletions [heterozygous/homozygous] included IKZF1 ( $n = 3$ ), CDKN2A/2B ( $n = 14$ ), PAX5 ( $n = 5$ ), and EBF1 ( $n = 1$ ) and STIL ( $n = 2$ ). B-ALL patient groups were IKZF1-Plus ( $n = 4$ ), IKZF1wt-other ( $n = 7$ ), and IKZF1-Plus absent ( $n = 9$ ). *Conclusion:* Our 850K CytoSNP-array was concordant with karyotype, FISH, or CGH + SNP array results and has been successfully validated of use in the diagnostic laboratory.

### P59. De Novo vs Relapsed vs Transformed Lymphoma – Assessing Clonal Relationship Using High-Throughput Sequencing

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Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma that accounts for 30%–40% of non-Hodgkin lymphoma cases. DLBCL usually arises de novo but can also arise from transformation of an indolent lymphoma. The unique immunoglobulin heavy chain (IGH) gene rearrangement of the malignant B-cell population can be used to determine clonal relatedness between multiple tumors from the same patient. In this case study, we present a patient diagnosed in 2005 with DLBCL in the right leg, who upon staging was found to have concurrent low-grade follicular lymphoma (FL) in the bone marrow. Following treatment with HyperCVAD, the patient achieved a complete remission. In 2019, the patient presented with mediastinal DLBCL with a mutational profile suspicious for transformed FL. A  $t(14;18)$  was detected using hybridization-based next generation sequencing (NGS). Mutations in *STAT6*, *CREBBP*, *TP53* and *KMT2D* were also detected. IGH gene rearrangement studies were performed by NGS using the Invivoscribe Lymphotrack IGHV Leader Somatic Hypermutation Assay Panel to assess the clonal relatedness to the previously detected DLBCL and FL. All three lesions shared a common IGH gene rearrangement (i.e. same V- and J-family usage). Homology analysis of the three IGH sequences was performed and was consistent with the leg and mediastinal DLBCL representing separate transformed subclones derived from an underlying persisting stem FL clone. The finding of likely two separate transformation events led the treating hematologist to opt for an allogeneic stem cell transplant in favour of autologous stem cell transplant in order to attempt to eradicate the stem FL clone.

### P60. Diagnostic Utility of CGH/SNP Microarray for Detection of Clinically Important Chromosome Abnormalities in Brain Tumors

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The 2016 WHO classification of tumors of the CNS and cIMPACT NOW Update 3 have highlighted the role of molecular diagnostics in improving accurate diagnosis and management of patients with brain tumors. Key copy number abnormalities are whole arm 1p/19q co-deletion in the diagnosis of oligodendroglioma, combined whole chromosome 7 gain/whole chromosome 10 loss (+7/–10) and/or EGFR amplification in the diagnosis of 'Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV', and BRAF-KIAA1549 rearrangement resulting from a duplication in 7q34 in the diagnosis of pilocytic astrocytoma. Traditional approaches using FISH are limited by the requirement for multiple tests, and the risk of a false positive result based on extrapolation from a limited number of loci. Our laboratory has implemented CGH/SNP microarray testing (CytoScan 750 K Array, ThermoFisher) to allow precise identification of clinically relevant copy number and copy number neutral LOH events. Our findings demonstrate the diagnostic utility of this platform to detect hallmark abnormalities, including whole arm 1p/19q co-deletion (9 cases), +7/–10 (23 cases), EGFR amplification (15 cases), duplication in 7q34 resulting in BRAF-KIAA1549 fusion (14 cases) and deletion in 7q34 resulting in BRAF-FAM31B (1 case). In addition, we have identified copy-neutral loss of heterozygosity (CNLOH) of 17p as a common abnormality in IDH mutation positive/whole arm 1p/19q co-deletion negative diffuse astrocytoma (23 cases), which correlates with the high frequency of TP53 mutations reported in this group. CGH/SNP microarray is a valuable tool, in conjunction with molecular mutation testing, in the classification of brain tumors.

### P61. NGS Implementation- the Experience of a Small Laboratory

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Next generation sequencing (NGS) is rapidly becoming incorporated into diagnostic laboratories across the globe. The implementation of this technology has led to a shift in the management of patients with leukemia. There is a requirement for centres to incorporate this technology into their workflow. The larger the throughput, the more economical this type of testing becomes as larger batch sizes can be handled. The downside to this technology is that testing becomes very expensive in smaller labs where the number of referrals is low. This is an issue for urgent referrals, particularly somatic cases where a fast result is often required in order to implement treatment. The detection of inactivation of TP53 plays an important role in disease management in patients with chronic lymphocytic leukemia as this is strongly associated with adverse prognosis and refractoriness to chemoimmunotherapy.

Our laboratory currently performs fluorescence in situ hybridization (FISH) for these patients. In this setting, FISH is only useful to detect deletions of TP53, whereas NGS has the ability to detect smaller, pathogenic variants. Thus, it is imperative that this testing is readily accessible and available with a reasonable turnaround time. We describe our experience with the validation process, the issues we encountered in order to implement sequence based testing within our laboratory and a workable solution for embedding this technology into our service.

### P62. The Value of Wes Data Re-analysis: De Novo CAMK2B Variant Causing Developmental Delay

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*CAMK2B* has recently been found to cause autosomal dominant intellectual disability 54 (MRD54-OMIM617799), characterized with global developmental delay, hypotonia, difficulty holding the head, delayed walking (or inability to walk) and speech (half of the patients are a verbal), behavioral problems, intellectual disability, visual impairment, gastrointestinal problems and facial dysmorphic features. Some patients have seizures with EEG changes and brain imaging is generally normal. We describe a 3-year old patient with global developmental delay recognized at an early age, characterized with hypotonia and inability to hold the head, lack of speech, inability to walk, seizures (controlled on anti-epileptic drugs) and behavioral problems. He is a second child from a third pregnancy of non-consanguineous parents with history of anencephaly in the first pregnancy and a healthy daughter. The parents embarked on a long and expensive diagnostic odyssey, including CMA and trio WES testing returning no result in late 2017. WES data re-analysis a year later identified a de novo pathogenic variant in *CAMK2B* (NM\_172079.2: c.709G>A), not present in the databases of human variation, predicted damaging by 'in silico' tools, affecting conserved amino acid residue and described previously in one other patient with MRD54 of different ethnic origin. The result helped end the diagnostic odyssey in this family and provided them with reassurance in terms of recurrence risk, but also addressed some longstanding misconceptions about 'likely X-linked condition/inheritance pattern'. This case illustrates the diagnostic utility of WES data reanalysis and importance of periodically revisiting uninformative results against growing evidence base for genetic causes of disease.

### P63. Maffucci Syndrome: Rare And Non-Inherited Cancer Predisposition Syndrome

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Maffucci syndrome (MS) and Ollier disease (OD) are rare non-hereditary cancer predisposition disorders, manifesting multiple

enchondromas with/without spindle cell hemangiomas, the latter serving as a distinguishing feature between the two conditions (present in MS, absent in OD). The tumors usually have an asymmetrical involvement and in about a third of cases enchondromas may undergo malignant transformation to chondrosarcomas. There is a variably increased risk of other malignancies, with incidence ranging from 5% to 50%, including glioma/astrocytoma, pancreatic/hepatic adenocarcinoma, breast, ovarian stromal tumor, and hematological malignancies. Recurrent mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) (p.R132C or p.R132H), or *IDH2* (p.R172S) are found in about 80% of tumors associated with MS/OD. A 57-year-old woman presented at age 6 years with bony swelling of left 4th digit, for which she underwent finger amputation at age 13. She subsequently developed multiple hemangiomas in left hand/forearm, revising her diagnosis from OD to MS. She had several hemangiomas removed from left breast and left hand/middle finger/wrist. Genetic testing performed on DNA extracted from paraffin-embedded tissue blocks from removed hemangioma identified the *IDH1* NM\_005896.3:c.394C>T (p.R132C) variant, which was absent in the blood DNA. She was offered annual whole-body MRI surveillance as part of a research study enrolling patients with multi-organ cancer prone syndromes. This case raised medical/ethical challenges concerning cancer risk management. The rarity of the condition limits the availability of evidence base to support development of clinical guidelines for cancer risk management and secure access to publicly-funded cancer surveillance tools (e.g. MRI).

### P64. Genetic Discrimination Concerns in Travel Insurance – The Pre-existing Medical Condition Rule

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*Background:* Internationally travel insurance remains unregulated in regard to genetic discrimination and has received little attention to date. A common question in applications relates to having 'Pre-Existing Medical Conditions' but an audit of Australian application forms did not identify genetic test results as criterion. *Aim:* to investigate the experiences of consumers who had had predictive genetic testing 2010–2016 and asymptomatic at the time of application for travel insurance. *Method:* Recruitment for an on-line survey was conducted through Australian support groups and research organizations. *Results:* 43/81 responses reportedly currently or past asymptomatic but at risk for hereditary cancer ( $n = 29$ ), cardiovascular ( $n = 3$ ), neurological ( $n = 9$ ), neuromuscular ( $n = 1$ ) and hereditary hemochromatosis ( $n = 1$ ) were valid for analysis. Travel insurance which is annually renewable was rated as important or very important by 81% compared to guaranteed renewable life insurance cover for death (63%), trauma (53%) or income protection (49%). All of the 19/43 respondents who applied for travel insurance reported concerns. 16/19 (84%) reported exclusion for claim for cancer (13) or cardiac conditions (3) imposed on the basis of having a pre-existing condition. Eleven of these respondents stated that they had answered yes to the pre-existing question which led to the insurance decision. Three others did not answer this question affirmatively but reported increased anxiety as a result. *Conclusion:* Given the importance of travel insurance to Australians, it needs to be emphasized to those

undertaking testing, healthcare providers and travel insurer providers that a positive genetic test result does not equate to having the condition.

### **P65. Decision-Making in Predictive Testing for Neurodegenerative Conditions: The QUEENSLAND Experience**

Jennifer Berkman

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Predictive testing for Huntington disease has been available since the discovery of the causative gene in 1993. Since then the genes responsible for many other neurodegenerative diseases have been identified, including familial motor neurone disease, CADASIL and the spinocerebellar ataxias. It has been well documented that predictive testing for these conditions should only be undertaken in the context of counseling by individuals trained in genetic counseling, to ensure the minimization of harm to the tested individuals. In Queensland predictive testing for these conditions is performed by both clinical geneticists and genetic counselors. This study reviewed the factors influencing decision-making of individuals who attended Genetic Health Queensland for predictive testing for neurodegenerative diseases from 2017 to 2018. Case examples illustrating the complexity of the decision-making process are also presented.

### **P66. Evaluation of Advantages and Challenges of Panel Testing in Cancer Genetics: A UK Case Report**

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

The management of HDGC/LBC family members is critical and complex. This case highlights the challenges presented in interpreting variants in families with no history of HDGC.

### **P67. Familial MND and FTD: Identifying the Need for a New Genetic Counseling Model of Care**

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

### **P68. Breast Screening in Young Women with NF1: Psychological Impact and Development of an Educational Resource**

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*Background:* Women with neurofibromatosis type 1 (NF1) have a moderately increased lifetime risk of developing breast cancer (18%); however, estimated 10-year breast cancer risks between ages 30 and 50 are comparable to those with *PALB2*, *CDH1* and *BRCA2* high-risk gene mutations. Consequently, EviQ guidelines recommend annual breast screening from 35 years. It is important to investigate the impact of breast screening, and provide appropriate support given NF1 is associated with learning difficulties and other cancer risks. *Aims:* (1) Assess the psychological impact of breast screening in young women with NF1. (2) Develop and evaluate an educational resource. *Methods:* Women with NF1 (30–47 years) enrolled in a single-centre pilot breast screening study were invited to: (1) complete patient-administered validated questionnaires

prospectively (including questions on experience) at four time points. (2) evaluate an educational brochure retrospectively via semi-structured telephone interviews. *Results:* Participant experiences ( $n = 21$ ) were mostly positive. Preliminary results suggest screening may lower clinically relevant anxiety and cancer worry (with some expressing reassurance), though these concerns may increase with recall. Most were satisfied with the screening process. Issues most frequently reported were discomfort, not being reassured and inadequate information regarding the process of additional testing for suspicious lesions. Barriers to future screening included fear of results and time off work. An easy-to-read brochure was developed, and evaluation is underway. *Conclusion:* Understanding psychological issues and barriers to screening in young women with NF1 will inform development of improved screening protocols and educational resources, to better support NF1 patients who undergo early breast screening.

### P69. Interesting Case Study: Termination of Pregnancy for Autism Risk

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

### P70. Predictive Testing in Minors and Non-disclosure, Should Testing Be Offered?

Lyndal Douglas, Janine Smith and Renee Sandells

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The issue of predictive testing in minors is always a contentious one; however, what are we to do as genetics professionals when a parent wishes to test their children and withhold disclosure of the results? This case highlights the difficulty of balancing the autonomy of children with the wishes of their parents. During the consultation regarding predictive testing for a cardiac condition, the parents disclosed their wish for predictive genetic testing and results to be given without the knowledge of their children. This presented challenges for our team regarding the autonomy of the children and their right to know/not to know, with attending to the parents needs and encouraging continued dialogue with the genetic team. Discussion of this case will include a summary of the literature surrounding predictive testing of minors and current guideline recommendations. Navigating the ethical complexities of this case will also be discussed.

### P71. Pilot Study of Expanded Preconception Carrier Screening in Western Australia – Health Professional Training and Perspectives

Samantha Edwards<sup>1</sup>, Royston Ong<sup>1</sup>, Georgina Hollingsworth<sup>1</sup>, Karen Harrop<sup>2</sup>, Denise Howting<sup>1</sup>, Sarah J Moore<sup>2</sup>, Ben Kamien<sup>3,4</sup>, Nicholas Pachter<sup>3,4</sup>, Mark Davis<sup>5</sup>, Karen Carpenter<sup>5</sup>, John Beilby<sup>5</sup> and Nigel G Laing<sup>1,5</sup>

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<sup>3</sup>Genetic Services WA, King Edward Memorial Hospital, WA Department of Health, Perth, WA, Australia, <sup>4</sup>UWA Medical School, University of Western Australia, Perth, WA, Australia and <sup>5</sup>Department of Diagnostic Genomics, PathWest Laboratory Medicine, WA Department of Health, Perth, WA, Australia

Expanded preconception carrier screening (EPCS) assesses the chance a couple will have a child affected with a recessive disorder. With the advent of new technologies it has become more affordable to sequence hundreds of disorders simultaneously. This pilot study aims to determine the requirements for successful implementation of a public health system EPCS program in Western Australia (WA). 250 couples planning to fall pregnant will be offered EPCS for more than 400 severe genetic disorders that are life limiting and/or chronic with onset in infancy or early childhood. Couples are recruited from the Perth and Busselton regions of WA through general practitioner, clinical genetic, and private genetic counseling services. Results are reported as a couple rather than individual carrier status. All recruiting health professionals (HPs) received training for pre-test counseling and the ability to offer EPCS specific to this pilot study and were further supported with resources including a pre-test counseling checklist and study information leaflet. General practitioners were observed by the study genetic counselor during their first pre-test counseling session with a couple. Training and support resources and HP perspectives were evaluated through a series of questionnaires and follow-up interviews. Analysis identified the knowledge, preferred methods of training, confidence in offering EPCS, expected versus actual barriers to recruitment, and informed choice of the different HPs performing pre-test counseling and recruiting to the study. While traditionally the responsibility of genetic professionals, it is possible for other HPs to offer EPCS to couples when provided with sufficient training and support resources.

### P72. Pilot Study of Expanded Preconception Carrier Screening in Western Australia – Lessons Learned

Samantha Edwards<sup>1</sup>, Royston Ong<sup>1</sup>, Georgina Hollingsworth<sup>1</sup>, Karen Harrop<sup>2</sup>, Denise Howting<sup>1</sup>, Sarah J. Moore<sup>2</sup>, Benjamin Kamien<sup>3,4</sup>, Nicholas Pachter<sup>3,4</sup>, Mark Davis<sup>5</sup>, Karen Carpenter<sup>5</sup>, John Beilby<sup>5</sup> and Nigel G Laing<sup>1,5</sup>

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King Edward Memorial Hospital, WA Department of Health, Perth, WA, Australia, <sup>4</sup>UWA Medical School, University of Western Australia, Perth, WA, Australia and <sup>5</sup>Department of Diagnostic Genomics, PathWest Laboratory Medicine, WA Department of Health, Perth, WA, Australia

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### **P73. 'Bridging the Gap' – The Value of Supervision in the Genetic Counseling Private Sector**

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<sup>1</sup>Parkville Familial Cancer Centre and Genomic Medicine, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia and <sup>2</sup>Monash Ultrasound for Women, Melbourne, VIC, Australia

As the profession of genetic counseling expands, more genetic counselors are working in private practice, which may include private enterprise such as general practice, obstetric ultrasound practice, and private laboratory services. Access to supervision is an important aspect of the working life of a genetic counselor, and may be particularly relevant in private practice with individual practitioners working in isolation. This study aims to explore the benefits and limitations of supervision for genetic counselors working in private practice. A semi-structured questionnaire was administered to 15 supervisees working in private practice in Victoria, Australia. They were asked about access to supervision, barriers and facilitators of the process, and perceived benefits. Questionnaire data was analyzed using both descriptive statistics, and inductive content analysis. The major barriers to supervision emerging from the data include: the employer's understanding of the value of supervision, cost, time and supervisor availability. Most supervisees had access to regular ongoing supervision. Those who had access reported it to be a valuable experience, with benefits both to themselves and individuals, as well as to their clinical practice.

### **P74. The Ins and Outs of a Regional Cancer Genetics Service; Review of Referral Handling and Triage Processes**

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<sup>1</sup>Mid North Coast Cancer Institute, Coffs Harbour, NSW, Australia and <sup>2</sup>Mid North Coast Local Health District, NSW, Australia

*Background:* Mid North Coast Local Health District (MNCLHD) include regional cancer genetics services in Coffs Harbour and Port Macquarie. Each service is staffed by one 0.5FTE genetic

counselor and the same visiting staff specialist (Cancer Genetics). *Aim/research question:* What is the current state of referral handling and triage processes in MNCLHD cancer genetics services and do we need to improve these processes? *Methods:* The current state of referrals was assessed by creating a cohesive data set and analysis of referrals received from 2016 to present. Current triage practice was assessed, national guidelines reviewed and information sought from other cancer genetic services, to ensure a best practice approach. *Results:* Since 2016, the number of referrals received in MNCLHD cancer genetics services has increased by 38%. Consistent recording of referrals and review of triage processes allowed for better understanding of services across the district. Comparison with other services in NSW and implementation of new triage guidelines demonstrate services are provided to clients within appropriate timeframes. *Discussion/Conclusion:* Regional genetics services encounter specific barriers of care, one being potential long wait-times for clients to see the visiting staff specialist. Discussion with other genetics services highlighted the different interpretations of triage and waitlist management, which prompted prioritizing the work of genetic counselors in waitlist management protocols. Review and analysis of referral data showed triage guidelines are fulfilled and clients are seen in appropriate timeframes. This reinforces the value and capacity of regional genetic counselors, addressing anxiety about equitable access to genetics services for regional clients.

### **P75. The VUS Odyssey in the Genetic Counseling Setting**

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While genetic technology allows us to look deeply into the DNA of individuals, it sometimes lacks the knowledge to interpret what we are seeing. Stumbling across a result where the clinical significance is unresolved leads us into the VUS territory – 'variant of unknown significance'. The detection of a VUS is the nemesis of the clinician, counselor and patient alike and can lead to what some have called 'genetic purgatory'. Undertaking genome sequencing in this era will always elicit VUSs and in January 2014 we commenced the Kids Heart Research DNA Bank research project (KHR DNA Bank) in Western Australia with the aim of capturing information on children undergoing surgery or diagnostic evaluation for congenital heart disease (CHD) at Princess Margaret Hospital for Children. With appropriate informed consent, DNA was collected from children and their parents with the purpose of undertaking whole genome studies to understand the underlying genetic causes of CHD. The VUS rate for the project was up to 69% so it is important to recognise the VUS will persist into the foreseeable future and plays an important counseling challenge in the research setting. Drawing on case studies from the research project, this poster presentation highlights the issue of disclosure, clarification, and duty to recontact when dealing with a VUS and thus the challenges faced from a genetic counseling perspective.

### P76. Review of Ethnic Inequalities in the Uptake of Non-invasive Prenatal Testing (NIPT) in Developed Countries

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International societies have emphasized equity of access is an essential component for the responsible introduction of Non-invasive prenatal testing (NIPT) into population-based screening programs. Social and cultural inequalities can impact on accessibility and uptake of NIPT, highlighting an underlying disparity in the utilization of NIPT. The multicultural nature of the Australian population challenges traditional approaches to the delivery of prenatal screening and testing programs, as practices of healthcare developed for the general population may be, to some extent, culturally inappropriate for a population of mixed ethnic backgrounds. Publications were selected for this review if they included the following criteria: (1) Sample: include women of ethnic minority; (2) Types of study: primary research or audits; (3) Language: English; (4) Publication dates: between 2008 and 2018. None of the reviewed publications were conducted in Australasia. Factors attributing to access and uptake of NIPT by ethnic minority women, include: (1) Language barriers and issues with medical interpretation; (2) Limited NIPT knowledge and awareness; (3) Health care professionals (HCP) not offering NIPT based on cultural stereotyping; (4) Lower educational levels; (5) Financial barriers: NIPT cost and health insurance coverage (6) Spiritual, religious and cultural attitudes towards prenatal diagnosis, disability and termination of pregnancy. This review emphasizes NIPT service provision alone cannot ensure equitable access of NIPT for a diverse population of women. HCP need education on NIPT counseling, and knowledge of ethnic minority women's ethno-cultural values, beliefs, health practices, and communication styles is essential to ensure equitable access to NIPT for ethnic minority women.

### P77. Making It Real: Students' Experiences of Simulation in the First Week of Genetic Counseling Education

Chris Jacobs, Sevasti Russell-Williams and Alison McEwen

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**Background:** The worldwide shortage of genetic counselors (GCs) impacts on students' clinical placement opportunities, in turn impacting on the rate at which the profession can grow to meet rising demand. Simulation immerses students in authentic experiences, providing safe opportunities to practice core skills and gain experiences that mirror clinical practice. **Aim:** The Master of Genetic Counselling program at UTS set out to develop authentic simulated clients (sims) for face-to-face or online education with the aim of exposing students to a range of situations and counseling skills right from the start of the program. We report on the development of the sims and students' evaluation of the sim workshop in Week 1 of the program. **Methods:** Using a co-design approach, six senior GCs with diverse expertise from across Australia took part in an online focus group, followed by individual Zoom meetings to inform the learning outcomes and develop the sims. Sims were checked for accuracy, authenticity and confidentiality by the contributing GC. Learning outcomes were to establish rapport and elicit sensitive information. All 24 students counselled two 'clients' played by professional actors with structured feedback from program staff, practicing GCs, actors

and each other. **Results:** Students rated the workshop extremely highly and commented that working with 'real' clients consolidated and extended their learning. Students learned from their own experiences and from watching others. Facilitators' feedback was highly valued. **Conclusions:** Simulation early in genetic counseling education provided students with authentic experiences that consolidated and extended their learning and mirrored genetic counseling practice.

### P78. One Size Doesn't Fit All. Genetic Counselor Reflections of Implementing Genomic Sequencing

Anna Jarmolowicz<sup>1,2</sup>, Gemma Brett<sup>1,2,3</sup>, Kirsty West<sup>1,4</sup>, Yana Smagarinsky<sup>1,2</sup>, Giulia Valente<sup>1,5</sup>, Emily Allen<sup>1,4</sup>, Yael Praver<sup>1,6</sup>, Ivan Macciocca<sup>2</sup> and Ella Lynch<sup>1,2</sup>

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As genomic sequencing (GS) technologies are increasingly utilized, consideration is needed to determine how best to integrate the technology into different medical disciplines. This includes consideration of how GS should be provided outside clinical genetics services, in particular how non-genetic health professionals can integrate GS into their clinical practice. There exists a gap in the literature regarding the clinical implementation of genomics at a service delivery level, particularly an exploration of the experiences of genetic counselors delivering GS within various healthcare models and in collaboration with non-genetic health professionals. Genetic counselors reflected on their diverse experiences of counseling for whole exome sequencing for a diverse range of medical conditions as part of a state-wide implementation project in Melbourne, Australia. Illustrative examples outline four different models of service provision; genetics outpatient, non-genetic specialist outpatient, multi-disciplinary outpatient, and inpatient. The successes and challenges of implementing genomics through these healthcare models were identified from the perspective of genetic counselors directly involved. Genetic counselors and other health care professionals will need to develop an awareness of the benefits and limitations of different healthcare models for the implementation of GS, and the need for flexibility in determining method of approach.

### P79. Experiences of Women and Their Partners Receiving Variants of Uncertain Significance Through Prenatal Chromosomal Microarray

Anaita Kanga-Parablia<sup>1,2</sup>, Joanne Kennedy<sup>3</sup>, Lydia Gaffney<sup>2,4</sup>, Tenielle Davis<sup>4</sup> and Susan Fawcett<sup>4</sup>

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We present the background and study design for a project currently in the data collection phase. Chromosomal microarray has significantly improved the diagnosis of chromosome conditions during pregnancy compared with conventional karyotype. However, this type of testing has led to an increased detection of 'variants of uncertain significance' (VUS). Existing research shows that receiving these uncertain results through chromosomal microarray during pregnancy may lead to women feeling shocked, confused or anxious.

Furthermore, there is limited research into the support they receive at this time. We aim to explore the experiences of women and their partners who received a VUS through prenatal chromosomal microarray and the role of genetic counseling in this setting. We will conduct semi-structured interviews with 10 to 15 women and their partners who received a VUS during pregnancy. Individuals will be recruited through the Royal Women's Hospital, Melbourne, VIC, Australia. Interviews will explore participant experience of receiving a VUS during and after pregnancy, how individuals cope with these results, and the role of genetic counseling in this setting. Interviews will be transcribed verbatim and we will use thematic analysis to identify themes within the data. This study aims to provide valuable insight into the experiences of women and their partners who have received a VUS through prenatal genetic testing, and the role of genetic counselors in supporting others receiving uncertain prenatal results in the future.

### **P80. Rapid Clinical Exome Sequencing in the Pediatric Intensive Care Unit: Challenges to Genetic Counseling**

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**Background:** Genomic sequencing has become widely available in clinical settings for diagnostic purposes. Since July 2018, rapid clinical exome sequencing (RapidSeq), focusing on known Mendelian genes, for critically-ill patients admitted to the neonatal or children's intensive care units (NICU or CICU) has been established in our institution. This retrospective review highlights challenges encountered by the genetic counselors (GCs). **Methods:** A standardized RapidSeq protocol has been established in our hospital. After the initial genetics assessment, the clinical geneticists will discuss the suitability for RapidSeq. If deemed suitable, pre-test counseling will be provided by a GC. Following sequencing, the genetics team will be involved in the variant classification and result reporting process. The result turnaround time is 10 working days. **Results:** Common challenges identified by GCs include obtaining informed consent, coordinating sample collection and managing caregiver expectations of genetic findings. The critical nature of RapidSeq requires effective coordination between the clinical team and laboratory. The pre-test counseling session is often impeded by multiple ongoing issues requiring parental attention. When other acute issues arise, sample collection is deprioritized and testing is delayed. The urgency for testing is often driven by the condition's severity, which guides prognostication. However, management of parental expectations regarding the prognosis can be challenging, including the explanation of possible result outcomes, which ranges from clear cut diagnoses to variants of uncertain significance and incidental findings. **Conclusion:** The awareness of highlighted issues enable GCs to better support families through the genomic sequencing process and implementation of RapidSeq at our institution.

### **P81. GC Chat, A Genetic Counseling Podcast: Reflections After Season 1**

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**Background:** The genetic counseling landscape is changing, with genetic counselors leading the transition of genomics into routine clinical care. We recognized an opportunity to raise greater awareness

of the counseling issues that can arise in genetic and genomic testing through an accessible, informative podcast. **Methods:** GC Chat, a podcast about the 'counseling' in genetic counseling, was launched in March 2019, and aimed at creating a platform for genetic health professionals, trainees and other interested parties to reflect upon the complex issues that can arise in genetic counseling. In each episode, a de-identified genetic counseling case is presented. Listeners then reflect and offer their insights on the presented cases through social media. In the following fortnightly episode, we reflect on the previous case, discuss the counseling interventions used and review supporting literature. **Results:** As of 1st May 2019, five episodes have aired with 1435 unique total downloads, and an international audience from 29 countries. Four cases and reflections have been published, encompassing the themes: misattributed paternity, non-disclosure, testing of children, and patient advocacy. Results from an online survey of listeners, designed to capture further insights from our audience, including the perceived effectiveness of this platform will also be presented. **Discussion and Conclusion:** Alternative means of accessing support and information is imperative as the genetic counselor role expands outside of the traditional clinical genetics unit. Podcasting is an effective way to provide an international and accessible platform for case reflection, evidence-based practice discussion and further education about the genetic counseling process.

### **P82. Imagining and Designing the Future of Genetic Counseling with the New Generation of Genetic Counselors**

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**Aims:** Genetic counselors (GCs) are leading the way in embedding the use of genetic and genomic information into routine health-care and facilitating the complex decision-making this requires. To develop students' future-orientation and their capacity to practice in this fast-evolving field we engaged them in co-designing Master of Genetic Counselling program at UTS. We report on the outcome of this first step within the program. **Method:** On their first day on campus, 24 first year students commenced their study by exploring current and future states of genetic counseling in a facilitated workshop using 'making', as a technique for collective sense-making. Underpinned by participatory co-design principles, 'making' involves teams creating a collective image of a problem space through the use of craft materials. 'Making' enables groups to tap into implicit knowledge and feelings about a given situation that can't be easily expressed in words. **Results:** Emergent themes articulated by students included (1) a strong desire for inclusivity and accessibility, with the benefits offered by precision medicine available for all; (2) an engaged public dialogue regarding genetics and genomics; (3) increased ability to utilise the massive amount of data generated; and (iv) continuation of person-centred genetic counseling practice. **Conclusions:** This collaborative exercise helped build rapport and empathy, creating a platform for ongoing dialogue between staff and students. Engaging students in a pro-active role of 'creating' the field from the outset positioned them as the future generation of GCs who are open to the possibilities and responsive to the complexity of a rapidly-changing profession.

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

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

### P84. Outcomes from a Trial of the GENETIC Psychosocial Risk Instrument in an Australian Genetics Service

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The Genetic Psychosocial Risk Instrument (GPRI) is a validated screening tool designed to identify psychological risk factors that predict distress in adults undergoing genetic testing ( $\geq 50$  indicates distress). Items examine experience of the genetic condition, impact of genetic testing and gene status, communication concerns, risk perception, and mental health history. The GPRI was as part of a study investigating the acceptability and feasibility of implementing the GPRI into clinical practice. It is the first Australian study to trial the GPRI as a pre-appointment screening tool. Patients ( $n = 154$ ) attending the

Parkville Familial Cancer Centre (FCC) and Genomic Medicine (GM) at Peter Mac and RMH were invited to complete the GPRI in the waiting room. The GPRI was scored and provided to the clinical staff prior to each appointment. Descriptive statistics and regression analyses were used. Of 145 participants (RR = 94%), 116 completed all GPRI items, with 25.5% reporting diagnoses of depression/anxiety or suicidal ideation (14.5%). The average GPRI score was 46.3 (95% CI [43.6, 49.0]) with 39% (34/88) of FCC and 46% (13/28) of GM patients scoring  $\geq 50$ . There were no differences in GPRI score between sites (FCC or GM), appointment type (new or review), and most demographic variables. However, women were three times more likely to score  $\geq 50$  compared to men (OR 3.1, 95% CI [1.2, 7.5],  $p = .02$ ), when controlling for site (FCC or GM), type of appointment (new or review), and age. The next steps are to investigate whether using the GPRI improves patient care, especially for female patients.

### P85. Uptake of Germline Genetic Testing in Patients with Ovarian Cancer in WA

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**Introduction:** Patients with non-mucinous epithelial tubo-ovarian cancers (NMEOC) should be referred for genetic testing because approximately 15% will carry an inherited mutation in the BRCA1/2 genes. However, referral rates for genetic testing remain low. For patients who carry a BRCA mutation, failure to refer for genetic testing results in missed opportunities for therapy and prevention of future cancers in the patient and at-risk relatives. In Western Australia between July 2013 and June 2015, 40.6% of patients with NMEOC discussed at a statewide gynecologic oncology tumor board were referred for genetic testing. Our objective was to investigate the proportion of patients with NMEOC in Western Australia referred for BRCA1/2 testing from July 2015 to December 2017, following the introduction of mainstreaming and telecounseling. **Methods:** Retrospective case series. All patients with high-grade NMEOC discussed at the weekly Western Australian gynecologic oncology meeting, between July 1st 2015 and December 31st 2017 were assessed. **Results:** Three hundred forty-three women were eligible for referral. Sixty-three patients were excluded leaving 280 patients for analysis. Two hundred twenty of 280 patients were referred for genetic testing (78.6%). There were no differences in uptake of genetic testing by mode of genetic counseling. **Discussion:** A significant increase in referrals of eligible patients for genetic testing was observed in 2015–2017 compared to 2013–2014. Although there were no differences in uptake of testing by mode of counseling, mainstreaming and telecounseling provide alternative options for patients that may lead to a higher uptake of genetic testing.

### P86. A Professional Development Tool Based on the 'Guidelines for Training and Certification in Genetic Counseling 2016'

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We are amidst a significant period for genetic counselors in Australasia, with the implementation of formal regulation of the

profession. It will soon be mandatory for associate genetic counselors to complete the training required for HGSA Board Certification. However, there is a lack of tools available to document, assess and reflect on professional growth within the genetic counseling profession. Recently, a study in Portugal was the first to validate a tool for quality assessment of genetic counseling services. This tool was based on the Reciprocal Engagement Model of genetic counseling, with 50 items to be completed on a scale of 1–5 following each consultation. We aim to create a professional development tool based on the 'Guidelines for Training and Certification in Genetic Counselling 2016' and the 'Scope of Practice for Genetic Counsellors 2018'. We envision this tool to have multiple uses: firstly, it could be used to assist with training new genetic counselors and identify their level of supervision needed; it could be used to identify areas of attention during individual supervision; lastly, the tool could be used to document competencies to be demonstrated during the certification process. Rather than focusing on evaluation, as does the Portuguese scale, the current tool focus on professional reflection and growth. We present a draft tool with 27 items, under competency standards of the Australasian certification guidelines. This tool uses a visual scale of 1–5, similar to the validated Portuguese scale. Validation of the current tool would be beneficial for wide-spread use in Australasia.

### **P87. Implementation of a Dedicated Ocular Genetics Clinic: A clinical Audit**

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The Royal Victorian Eye and Ear Hospital (RVEEH) is Australia's only quaternary referral centre of its kind. However, genetic testing for patients with inherited eye disease typically occurred through clinical genetics services based at other 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 RVEEH have initiated a combined multidisciplinary Ocular Genetics Clinic based at the RVEEH to address this need. The service is comprised of ophthalmologists, orthoptist, clinical geneticist and genetic counselor. Here we aim to present the results of a clinical audit of the first 6 months of this specialized clinic. A retrospective audit of the families seen including clinical diagnoses, ophthalmic investigations, genetic tests ordered, results and outcomes covering the period between December 2018 and July 2019 was conducted by reviewing the medical records. In the initial 3-month period, 37 patients have attended OGC with the majority having a differential diagnosis of retinitis pigmentosa (16/37), followed by optic atrophy (6/37) and macula dystrophy (3/37). Overall, twenty-two patients underwent genetic testing. Additional results over the 6 month period, as well as the diagnostic utility of such testing, will be presented. Implementation of the OGC in a quaternary setting is expected to provide timely service and increase patient satisfaction in a field

where treatment strategies are evolving rapidly, and are heavily dependent on an accurate genetic diagnosis.

### **P88. Evidence, Education and Encouragement – Implementation of a Laboratory-Based Genetic Counselor**

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The Royal Children's Hospital (RCH) in Melbourne, VIC, Australia appointed two laboratory-based genetic counselors (LBGCs) mid-2017, employed by the Victorian Clinical Genetics Services (the clinical genetics service of RCH) for a three-year full-time job-sharing role. LBGCs aim to facilitate access to high-quality, cost-effective, clinically indicated and accurate genetic and genomic testing through a hospital-wide systematic approach. This has been achieved by overseeing the test request review process which assesses tests according to their clinical utility. Information collected via a LBGC-designed REDCap database allows for evaluation of the LBGC role in actioning requests, analysis of departmental ordering trends, diagnostic yields and cost-savings, for both laboratory services and the broader hospital. Undertaking just-in-time education sessions with medical specialists, providing readily accessible ordering information and advice, as well as inviting regular requestors of genetic tests to the monthly genetic review meetings has meant a decline in inappropriate/likely low yield test requests and an increase in appropriate referrals to genetics. Alternative pathway funding has facilitated collaboration with the Neurology department, facilitating upskilling of clinicians and, in the near future, the opportunity to undergo appropriate 'credentialing' in genetics and genomics, reinforcing the importance of its implementation into broad clinical practice. Significant disruptive changes in test ordering are imminent, namely a Medicare item number for whole-exome sequencing which will allow ordering by non-genetic specialists, that will naturally challenge the LBGC role. However, evidence to date is encouraging that the LBGC will adapt and continue to guide and support effective service delivery.

### **P89. Genetic Counselor, Patient and Carers' Views on the NSW/ACT Clinical Genetics Service Information System**

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The Genetic Information System (GIS) is a database of family genetic information used by New South Wales (NSW) and Australian Capital Territory (ACT) clinical genetics services. In this study, we explored genetic counselors' experiences of the GIS, and patients'/carers' views about family genetic information being stored in the GIS and used for the healthcare of relatives. Semi-structured telephone interviews were conducted with experienced genetic counselors employed in public NSW & ACT clinical genetics services, followed by focus groups with past patients/ carers of these services. Both data sets were audio-recorded, transcribed and analyzed using

thematic analysis. Twelve genetic counselors were interviewed identifying four themes: (1) Shared information is valuable; (2) Inconsistent data entry provides a challenge; (3) Perceived need for the GIS to be current and integrated with other health systems; and (4) Future challenges and strategies for the GIS. Subsequently, three focus groups were held with 14 patients/carers, identifying three further themes: (1) Access to family genetic information provides a 'clearer picture'; (2) Support, but caution, about using information for relatives' healthcare; and (3) Stewardship of family information. Genetic counselors and patients/carers identified advantages and privacy concerns regarding the sharing of family genetic information. Patients/carers were reassured by genetics health providers' stewardship, but all participants wanted patients/carers to be better informed about the GIS early in the genetic counseling process. We hope these findings will guide improvements to the utility of the GIS; and to greater patient/carer knowledge through further development of patient resources.

### **P90. Achieving a Moratorium on the Use of Genetic Test Results in Insurance in Australia**

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

### **P91. Where's Wally? Genetic Counseling and Identifying New Cases in Families with Fabry Disease**

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Fabry disease is a rare, X-linked inherited disorder affecting different body systems. Given the range of disease presentation, people's lack

of awareness about the condition, and its presence in their family, Fabry disease can often go misdiagnosed or undiagnosed. This program aimed to establish a national genetic counseling and testing service for families where the Fabry disease proband has been identified. Patients with Fabry disease were referred to the Fabry Genetic Support Service (FGSS) by their Fabry clinician. Following intake, genetic counseling was provided via telephone in which a family tree was constructed to identify at risk family members. Cascade testing was carried out within these families, with genetic counseling and testing was offered to at risk individuals. While some patients had good knowledge of Fabry disease and its inheritance, and had spoken with their families, others required updated information and assistance in reaching out to family members with whom they had little or no contact. To date, 61 probands have been referred to the FGSS from WA, QLD, NSW and SA. Ninety-four individuals from 33 families have been engaged within the program by overcoming many obstacles. Genetic counseling was provided to 94 individuals and testing organized for 35 individuals. Interestingly, several cases were found where only the proband was a carrier and the condition unexpectedly arose as a new genetic mutation. This program has been successful in reaching families across Australia and providing dedicated counseling, education and testing for individuals at risk of Fabry disease.

### **P92. Breaking Tradition: Delivering a National NIPT Genetic Counseling Service Via Telephone**

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Traditionally, genetic counseling has been offered face-to-face for at risk individuals and families. A telephone-based genetic counseling model potentially offers increased convenience, wider reach, quicker turnaround around times and a more accessible service. This program aimed to provide a high-level genetic counseling service for non-invasive prenatal tests (NIPT) in a convenient, accessible and timely manner to patients across Australia. Genetic counseling was offered as a complimentary service for all high-risk results returned using the Generation NIPT. Health professionals who ordered the original test were able to refer patients on to genetic counseling, and these patients were subsequently contacted via telephone for the delivery of counseling. The NIPT telephone counseling service engaged all individuals referred except one. Genetic counseling was delivered in a quick and efficient manner (95% of cases within 48 h), reaching patients based in both metropolitan and rural locations. While both GP's and specialists referred patients for counseling, the majority of tests were ordered and referred on by GP's. Referrals were received for all the different aneuploidies detected by NIPT, with trisomy 21 constituting the highest percentage of tests ordered and high-risk results received but having one of the lowest rates of referral for counseling. Aneuploidies involving the sex chromosomes were more likely to be referred on for counseling than those involving autosomes. This model of genetic counseling has proved successful in delivering a high quality, accessible and convenient service across Australia. The program is being utilized by health professionals to assist them in supporting their patients.

### P93. Pharmacogenomics as an Element of Precision Healthcare: The St Vincent's Experience

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

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

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**Background:** In the setting of hypertrophic cardiomyopathy (HCM), genetic results provide invaluable information, allowing at-risk relatives to undergo predictive testing. Communication to at-risk relatives is currently not ideal, with 20%–40% of relatives uninformed about relevant genetic information. **Aim:** Improving knowledge of a genetic result may positively impact on communication to at-risk relatives. We aimed to determine if a genetic counselor-led intervention using a communication aid for delivery of HCM genetic results improves ability and confidence. **Methods:** This was a prospective randomized controlled trial. Consecutive HCM patients were invited to participate. Once consent was obtained they were randomized to receive their genetic result via the intervention (with communication

aid) or control arm (usual care). Primary and secondary outcomes were measured using a survey comprised of a number of validated scales. The primary outcome was the ability and confidence of the proband to communicate genetic results to at-risk relatives. **Results:** The a priori primary outcome did not show statistically significant differences, though the majority of probands in the intervention group achieved good communication (13/22 [59%] vs. 10/20 [50%],  $p = .26$ ). Genetic knowledge scores were consistently higher among the intervention group (19/22 [86%] vs. 12/20 [60%],  $p = .05$ ). Importantly, among the cohort we found 29% of at-risk relatives were not informed of a genetic result. **Conclusion:** We show evidence that a communication tool has a positive impact on family communication. Research to further develop this to support communication in HCM families is needed.

### P95. 'Classical' Maple Syrup Urine Disease (MSUD), Lifespan Leucine Levels and Natural Protein Tolerance

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**Background & Aim:** Retrospective chart review and data analysis was conducted to determine lifespan leucine levels and natural protein tolerance, of 9 children with classical MSUD (6 male, 3 female), diagnosed/managed by The Children's Hospital at Westmead – Metabolic Service, between January 1999 and October 2017. **Outcomes:** At diagnosis, peak leucine levels ranged from 879–4359  $\mu\text{mol/L}$ , 89% underwent continuous veno-venous hemofiltration. One child died as a neonate. At 3 years of age, 3 underwent gastrostomy insertion, due to poor adherence of supplement, when well and unwell. Three underwent liver transplantation, following which their leucine levels were excluded from analysis. Age at end of study was 6–18 years. Excluding initial diagnosis admission, median leucine levels for the cohort ranged from 182–372  $\mu\text{mol/L}$ , peak being 1050–2262  $\mu\text{mol/L}$ , with 16% of leucine readings being >600  $\mu\text{mol/L}$ , often associated with intercurrent illness/catabolism or excessive natural protein intake. Thirty percent of samples, measured a normalized leucine level (56–201  $\mu\text{mol/L}$ ). On average patients had 48 leucine levels measured/year (range 19–81), this includes levels during the recovery phase following elevated levels. Prescribed natural protein intake varied between patients, based on phenotype and intrinsic enzymatic activity, with patients tolerating between 4.5–8 g/day. **Conclusion:** Several families and patients struggled with adherence to treatment, with frequent fluctuations in leucine levels. The introduction of dried blood spot leucine monitoring in 2010 allowed for more timely and frequent monitoring, both routine and when unwell. However, even closer and more frequent monitoring of leucine levels, with constructive feedback to families, may assist with increasing the percentage of normalized leucine levels.

### P96. Steroid Profiling by LCMSMS Improves Screening for Congenital Adrenal Hyperplasia in New Zealand

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**Background:** Congenital Adrenal Hyperplasia (CAH) is an inherited disorder of cortisol and aldosterone biosynthesis. Newborn

screening is available in New Zealand (NZ) as early recognition and treatment can prevent serious morbidity and mortality. Screening is by measurement of bloodspot 17-hydroxyprogesterone (17OHP) by immunoassay. Screening is generally sensitive but the false positive rate (FPR) is high due to interference from other steroids. Steroid profiles in bloodspots by liquid chromatography mass spectrometry (LCMSMS) has the potential to reduce the FPR and false negative rate (FNR) in CAH screening. *Methods:* All newborn screening samples with an out of range 17OHP result by immunoassay were subjected to a second tier LCMSMS steroid profile method. The screening test was considered positive if the LCMSMS result was out of range and if a further sample was not expected. Newborn screening data was used to determine CAH screening metrics prior to and after introduction of LCMSMS. *Results:* Assay precision, accuracy, linearity and recovery were acceptable. LCMSMS bias for 17OHP was  $-8.3\%$ . The PPV of CAH screening 2010–2017 was 2.09% (455,935 screens, 14 CAH cases) with a FPR 0.15%. The PPV in 2018 was 12.5% (58,953 screens, 2 cases) with an FPR of 0.02% ( $\chi^2$  test,  $p < .0001$ ). Out of 7 missed cases, 5 had steroid profiles consistent with CAH in the neonatal period. *Conclusions:* LCMSMS analysis significantly reduced the FPR of newborn screening for CAH without any changes to any other aspect of the laboratory protocols. LCMSMS has the potential to improve sensitivity if appropriate protocol changes are implemented.

### P97. Findings of a 12-Month Audit of Adult Patients with Phenylketonuria

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*Background:* As the first generation to benefit from newborn screening, children diagnosed in the 1970's with PKU were treated with amino acid preparations and dietary protein restriction. In keeping with the consensus at the time, dietary management was relaxed from age 6 to 9 years. We describe a 12 month audit of 22 adult PKU patients with temporarily treated PKU who have re-engaged with the metabolic service. *Aim:* To investigate the characteristics of adult PKU patients, including gender and engagement over a 12month period. *Methods:* A 12-month retrospective audit was completed on adult patients aged 40–49 years who were diagnosed shortly after birth with PKU, and treated to metabolic goals, with relaxation of therapy in subsequent years. Patients following pregnancy protocols were excluded. The following were examined; gender, number of Guthrie cards completed, phenylalanine levels and clinic attendance. *Results:* Analysis of this patient group revealed 4 males and 18 females. Guthrie cards were completed by 10 (8 female, 2 male) patients and clinic attendance showed 12 (10 female, 2 males) patients. In the 10 patients who submitted an average of 7 Guthrie cards, plasma phenylalanine levels averaged 764.2  $\mu\text{mol/L}$ . Clinic notes indicate that most were following dietary prescription with amino acid preparations. *Conclusion:* Study of this patient group informs program planning, in particular recognition that adult male PKU patients have mostly remained unengaged with metabolic services. The greater numbers of females compared to males we interpret to reflect the effect of reintroduction of the dietary treatment for pregnancies in previous years.

### P98. Liver Transplantation in Children with Inborn Errors of Metabolism: 30 Years' Experience in NSW, Australia

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*Background:* Inborn errors of metabolism (IEM) are a diverse group of disorders that can result in significant morbidity and even death. Metabolic management can be challenging and burdensome for families. Liver transplantation (LT) is increasingly being considered a treatment option for some IEMs. IEMs are now considered the second most common reason for LT. *Aim:* To review the data of all children with an IEM who had undergone LT at The Children's Hospital at Westmead (CHW), NSW between January 1986 and January 2019. *Methods:* Retrospective data collected from the medical records and genetic files included patient demographics, parental consanguinity, family history, method of diagnosis of IEM, hospital and intensive care unit admissions, age at LT, graft type, clinical outcomes and metabolic management post-transplant. *Results:* 24 liver transplants were performed for 21 patients. IEM diagnoses were MSUD ( $n = 4$ ), urea cycle disorders ( $n = 8$ ), organic acidopathy ( $n = 6$ ), tyrosinemia I ( $n = 2$ ) and GSD Ia ( $n = 1$ ). Three patients had repeat transplants due to complications. Median age at transplant was 6.21 years (MSUD), 0.87 years (UCD), 1.64 years (OA) and 2.2 years (Tyrosinemia I). Two patients died peri-operatively early in the series, one died 3 months after successful transplant from line sepsis. Eighteen LTs were performed since 2008 in comparison to six LT before 2008. Dietary management was liberalized post LT for all patients. *Conclusion:* Referral for LT for IEMs has increased over the last 33 years, with the most referrals in the last 10 years. Early LT has resulted in improved outcomes and survival.

### P99. A Case of an Unusual Pathway for Diagnosis of CAH

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*Background:* Since May 2018 New South Wales (NSW) has included screening for congenital adrenal hyperplasia (CAH) as part of routine newborn bloodspot screening. Samples with 17-hydroxy progesterone (17 OHP)  $>22$  nmol/LWB ie above the 98th percentile are further tested with steroid profiling by MSMS. Those with an abnormal profile have repeat bloodspot and diagnostic samples requested. *Aim:* To present a case with a less than ideal pathway. *Methods and Results:* Samples were collected for twins (twin 1 male, twin 2 female) aged 58 h. The samples were received late day 7, screened by immunoassay for 17 OHP, followed by confirmation using MSMS with 17OHP 172.3 nmol/L for twin 2, and 2.8 nmol/L for twin 1. Diagnostic samples were requested day 9, and blood spot 17OHP confirmed these results as did electrolytes, showing classical salt-wasting in twin 2, and normal results for twin 1. Twin 2 was placed on treatment. However plasma samples collected for diagnosis were unsuitable due to improper handling, and analyzed only for cortisol using an immunoassay (in error).

This gave elevated cortisol levels for twin 2 (700 nmol/L) inconsistent with a diagnosis of CAH. In order to determine whether twin 2 had CAH, treatment was ceased and serial samples collected: day 1 off treatment – normal; day 2 – consistent with CAH, bringing about deterioration of the baby's condition. Treatment recommenced. *Discussion/Conclusion:* This case demonstrates the importance of not only including screening for CAH as part of a newborn screening programme but that follow-up protocols must be strictly followed.

### P100. An Infant Presenting Clinically with CPTII Deficiency Which Was Missed by Standard Newborn Screening

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The Queensland Newborn Screening Programme tests approximately 65,000 births per year. This abstract presents a male infant, presenting in the first day of life with symptomatic hypoglycemia (glucose 1.1 mmol/L). The baby did not pass urine for 8 h after the event consistent with poor breast milk intake. An acylcarnitine collected as part of the hypoglycemia screen was diagnostic of carnitine palmitoyl transferase type II (CPTII) or carnitine-acylcarnitine translocase deficiency (CACT)-: Palmitoylcarnitine (C16): 4.1 μmol/L (<0.74), Oleoylcarnitine (C18:1): 2.78 μmol/L (<0.27); acetylcarnitine (C2): 14 μmol/L (1–13) and (C16 + C18:1)/C2 ratio 0.59 (<0.1). The infant was treated with intravenous 10% dextrose therapy. He was well but still on intravenous dextrose in addition to breast feeds at time of collection of the newborn screening sample, at 52 h of age, which was normal. Currently our newborn screening program only recommends notification of the absence of lactose containing feeds for infants on intravenous glucose. Repeat acylcarnitine profile on day five when on oral feeds showed C16: 0.8 μmol/L, C18:1: 0.73 μmol/L (<0.27) and (C16 + C18:1)/C2 was 0.26 (<0.1). DNA testing showed two pathogenic variants, c.1511C>T (p.Pro504Leu) and c.338C>T (p.Ser113Leu) in the CPT2 gene. *Conclusion:* This case shows that parenteral glucose can impact on newborn screening results and increase the chance of missing some infants affected with a fatty acid oxidation disorder. We suspect that the mild or later onset fatty acid oxidation disorders are most at risk of being missed and these may also be missed if newborn screening was repeated several days later.

### P101. Modelling the Mitochondrial Disease Sengers Syndrome Using Human Embryonic Stem Cells

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*Background:* Sengers syndrome is a potentially fatal mitochondrial disease characterized by hypertrophic cardiomyopathy, congenital

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

### P102. Impact of MDDA Retreat on Short-Term PHE Levels of a Sub-Group of Adult PKU Patients

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Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism (IEM) resulting from the deficiency of phenylalanine hydroxylase. To prevent neurological damage, lifelong adherence to a low-phe diet and supplementation with a phe-free amino acid formula is required. This remains a significant challenge to those with PKU, especially patients returning to diet as adults. This project aimed to determine if there was significant change in phe levels following attendance at the Metabolic Dietary Disorders Association (MDDA) second WA Retreat in March 2019. All adults with PKU attending RPH IEM Clinic were invited to attend via email. Twelve patients attended the Retreat and 11 had phe monitoring after. Of these 11 patients, three were men; average age 44 years. Average phe level prior to the retreat was 922 μmol/L (range 479–1675 μmol/L) and after was 704 μmol/L (188–1316 μmol/L). Nine patients recorded phe levels lower than their pre-retreat level ( $p = .007942$ ). Attendees stated education sessions, peer support and availability of low protein foods as possible reasons for improved levels. Adherence has previously been reported to improve if individuals have a social support system; an understanding of the benefits of treatment; access to appropriate care, medical foods and modified low protein foods and belief that PKU is manageable. The next phase of this project will involve engaging these patients to maintain their improved phe levels. Dietitian-lead small group sessions will be investigated and planning to increase attendance at the next MDDA WA retreat.

### P103. Newborn Screening for GA1 by Underivatized MSMS: Improved Sensitivity and Specificity Using LCMSMS

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**Background:** Glutaric aciduria type I (GA1) is a rare autosomal recessive organic aciduria, which frequently remains undetected prior to an encephalopathic crisis. There are two clinically similar subgroups of GA1: Low excretors, which show a relatively low bloodspot of concentration glutarylcarnitine (C5DC), and high excretors, which show a consistently high concentration. However, the concentration of C5DC does not predict the severity of the phenotype. Pre-symptomatic detection and early treatment offers improved outcome and newborn bloodspot screening for GA1 by measuring C5DC using MSMS is well established. **Aim:** Sensitive NBS detection of low excretor GA1 requires a relatively low C5DC detection limit (DL). However, under MSMS underivatized conditions, C5DC is isobaric with abundant 3-hydroxyhexanoylcarnitine (C6OH), which makes analytical specificity poor. Sample reanalysis using derivatized (butylated) methods may be used. However, C5DC is then isobaric with 3-hydroxydecanoylcarnitine, which may then require LCMSMS to resolve. **Method:** We describe a rapid, simple liquid chromatography MSMS (LCMSMS) method using an amide column to separate of C5DC and C6OH by direct reanalysis of the initial NBS underivatized sample extract. The 5-min LC method resolves the C5DC and C6OH, which can be individually quantified using standards. The use of hazardous solutions for butylation is avoided. **Conclusion:** Sensitivity for LE type GA1 is improved by using a low initial DL for C5DC and routine second-tier LCMSMS analysis. Detection of a case of GA1 type LE is discussed.

### P104. A Neonate with an Acute Presentation of Glutaric Aciduria Type II with Maternal Liver Disease

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Maternal liver disease has been reported to be more frequent in women carrying a foetus affected by a fatty acid oxidation disorder (FAOD). We report a day three infant who presented acutely with hypoglycemia and high anion gap metabolic acidosis. The pregnancy had been complicated by maternal hypertension progressing to pre-eclampsia from 36 weeks then maternal hemolysis, elevated liver enzymes and a low platelet count (HELLP syndrome) at 38 weeks. The mother required platelet transfusions before and after delivery. A female infant, delivered by planned caesarean section, was initially well. At 48 h of life, the infant became anorexic, lethargic, tachypnoeic and 4 h later rapidly deteriorated with hypoglycemia, hyperammonemia, metabolic (mainly lactic) acidosis, mild liver transaminitis, coagulopathy, hyperuricemia and uremia. She responded quickly to cessation of protein feeds and intravenous 10% dextrose/normal saline infusion. Rapid acylcarnitine analysis diagnosed glutaric aciduria type II (GAII). Intravenous fluids were continued for 48 h with a gradual increase in oral feeds with fat initially restricted to 25% of calories. Repeat acylcarnitine profile after

48 h of therapy was normal and the fat restriction is being gradually eased. The mother recovered over 5 days and her acylcarnitine profile was also normal. **Conclusion:** Although the association between foetal FAODs and maternal liver disease is debated by some, in this case the maternal HELLP syndrome directed the clinicians to prioritise testing for a FAOD. We cannot find a previous publication on the association of maternal liver disease and glutaric aciduria type II.

### P105. Time-Of-Flight Mass Spectrometry Analysis of Transferrin for Screening N-linked Congenital Disorders of Glycosylation

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**Background:** Congenital disorders of glycosylation (CDG) encompass a large group of inherited multisystem disorders, which are characterized by defective glycosylation. Over 100 CDG have been described but this number is expected to rise, with more than 400 genes known to be involved in glycosylation pathways and almost half of all proteins synthesized glycosylated. The best characterized CDG involve N-linked glycosylation. Transferrin, a glycoprotein present in blood to transport iron, has predominantly two bi-antennary N-linked oligosaccharides. Defective glycosylation results in absence, or reduction in the monosaccharides comprising the glycan chain. Examination of transferrin isoforms can identify impaired N-linked glycosylation and is established as the biochemical marker for N-linked CDG. **Aim:** Develop a time-of-flight (TOF) mass spectrometry method, which is able to provide the detailed glycan structure of transferrin. **Method:** Direct injection of serum, incubated with ammonium bicarbonate and dithiothreitol onto an Agilent 6230 TOF LC/MS instrument with electrospray ionization source, connected to an Agilent 1260 binary pump. **Results:** The 4-sialo transferrin isoform, representing transferrin with two complete bi-antennary oligosaccharide chains attached, is the major component observed for normal individuals. Satellite isoforms correspond to 5-, 4-, 3- and 2-sialo components. Abnormal transferrin isoform patterns can readily be distinguished by TOF mass spectrometry, which is highly sensitive and distinguishes between loss of an entire glycan chain, or individual monosaccharides. **Conclusion:** TOF mass spectrometry analysis of transferrin provides detailed structural information for transferrin isoforms, enabling assessment of transferrin glycosylation to determine when N-linked glycosylation pathways may be impaired, indicating a potential CDG case.

### P106. Time-Of-Flight Mass Spectrometry Analysis of Apolipoprotein CIII for Screening O-Linked Congenital Disorders of Glycosylation

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**Background:** Glycosylation is an important co- and post-translational modification of proteins, conferring significant and diverse functionality. Congenital disorders of glycosylation (CDG) are inherited multisystem disorders characterized by defective glycosylation. CDG are defined by the glycosylation pathway affected and impaired glycan type. Clinical presentation for O-linked CDG involve a variety of symptoms but can include muscle, eye and brain

phenotypes making diagnosis difficult. Apolipoprotein CIII (Apo CIII) is a plasma protein and component of triglyceride rich lipoproteins, including VLDL. Apo CIII has a single O-linked oligosaccharide chain, representing the most common type of mammalian O-glycosylation and established as the biochemical marker for O-linked CDG. *Aim:* Develop a time-of-flight (TOF) mass spectrometry method able to provide the detailed glycan structure of Apo CIII. *Method:* Ultracentrifugation of plasma to isolate VLDL fraction for direct injection onto Agilent 6230 TOF LC/MS instrument with electrospray ionization source, connected to an Agilent 1260 binary pump. *Results:* The 1-sialo Apo CIII isoform, representing Apo CIII oligosaccharide with one terminal sialic acid, is the major component observed for normal individuals. Satellite isoforms correspond to 2- and 0-sialo components. A reduction in highly sialylated and increase in less sialylated components can be indicative of a CDG as a consequence of impaired O-linked glycosylation, resulting in alteration of the Apo CIII isoform pattern. *Conclusion:* TOF mass spectrometry analysis of Apo CIII provides detailed structural information for Apo CIII isoforms, enabling assessment of Apo CIII glycosylation to determine when O-linked glycosylation pathways may be impaired, indicating a potential CDG case.

### P107. BH4 Responsiveness Testing: Practical Pitfalls

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Sapropterin (BH4) has been approved for listing on the Pharmaceutical Benefits Scheme for children with Phenylketonuria (PKU) in Australia. There is expected to be a requirement to prove responsiveness to BH4 prior to prescription with blood phenylalanine (Phe) levels >600 µmol/L before trialling BH4. This case study describes dietary modification prior to planned BH4 loading in a 17 year old male with PKU, with a baseline protein allowance of 5 g/day and intake of 80 g protein equivalent (PE) from protein substitutes. The patient completed 3 dry blood spots (DBS) over 2 weeks prior to BH4 loading to establish his baseline Phe levels. Baseline Phe results ranged from 430–575 µmol/L. On days 1, 9, 15, 17 and 22 of the trial, protein from food was increased to 110%, 130%, 160%, 200%, and 300% of baseline intake, respectively. PE was decreased to 60 and 40 g on days 17 and 22. DBS monitoring occurred regularly throughout the trial. Despite gradual increases in protein from food and reductions in PE from protein substitutes, a sufficient increase in Phe necessary to demonstrate responsiveness was not observed, with Phe levels ranging from 158–593 µmol/L across the trial period. This patient demonstrated greater protein tolerance than expected in the lead up to this load test. We suspect baseline natural protein intake for this patient was underestimated. It would be useful in future to obtain an accurate indication of protein intake via food diaries prior to responsiveness testing for other children.

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

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

### P109. Two Children with Organic Acidurias and a Fish-Like Odour Treated with Riboflavin

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We report two girls, the first with a diagnosis of glutaric aciduria type I and the second with vitamin B12 responsive methylmalonic aciduria, who had both developed the fish-like odour of trimethylaminuria caused by L-carnitine supplements. L-carnitine is metabolized to trimethylamine (TMA) by intestinal flora and then to trimethylamine oxide (TMAO) by the liver enzyme, flavin monooxygenase 3 (FMO3). There is a lot of interindividual variation but up to 50% of the L-carnitine is converted to TMA. TMA but not TMAO causes the fish-like odour. *Methods:* Baseline TMA was elevated in both patients. Riboflavin (vitamin B2) 100mg/day was prescribed. Both sets of parents reported the disappearance of the odour within three days of supplementation. Biochemical testing confirmed that TMA levels greatly reduced but were still above the normal range after several weeks of riboflavin therapy. Patient 1: baseline 23.76 mmol/mol creatinine then post treatment 2.77 mmol/mol creatinine (RR <2.0). Patient 2: baseline 134.9mmol/mol creatinine then post treatment 27.98 mmol/mol creatinine (RR<2). There was an 88% and 79% reduction in TMA in patients 1 and 2 respectively and a 29% and 83% reduction in their respective TMA/TMAO ratios consistent with upregulation of FOM3 enzyme activity in response to the riboflavin therapy. One child ceased her riboflavin and the odour returned within a week. *Conclusion:* Treatment with riboflavin can reduce the odour caused by trimethylamines from carnitine supplements in patients with organic acidurias. The children and parents are delighted with the outcome. Larger studies should be considered to provide further evidence of efficacy.

### P110. Carnitine Palmitoyltransferase Deficiency – A Difficult Disorder for Newborn Screening

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*Introduction:* Carnitine palmitoyltransferase II (CPT II) deficiency is a long-chain fatty-acid oxidation disorder with different clinical presentations: lethal neonatal form, severe infantile hepato-cardio-muscular form, and later onset rhabdomyolysis or myopathy. *Case report:* A female infant identified through newborn screening was reviewed at 3 weeks of age, indicating normal growth and

development on breast feeds. A feeding plan including breast milk and formula high in medium chain triglycerides (MCT) was commenced. Subsequent biochemical studies including plasma acylcarnitine analysis, urine organic acids, and cultured fibroblast acylcarnitine analyses were done. CPT II enzyme studies on blood (3% of controls) and fibroblasts (5% of controls) confirmed this diagnosis. At three months of age, after a short history of MCT feed refusal and a respiratory infection, she presented with hypoglycemia, initially responsive to glucose infusion. She subsequently had an unresponsive episode with hypothermia, mild acidosis and ammonia elevation. She responded to beta-hydroxybutyrate (ketones) and hyper-hydration with dextrose-saline. Her serum ammonia levels improved, from 304 to 38 umol/L, (ref range: 10–50 umol/L) and she had normal neurology and brain MRI after recovery. Whole exome sequencing showed a likely pathogenic c.136C>T p.(Gln46\*) variant and one VOUS c.371G>C p.Arg124Pro in the CPT2 gene (phase unknown). Genetic counseling was recommended for future family planning. At her most recent visit aged 6 months, development appeared normal with some concern about swallow functions. *Conclusion:* It can be difficult to determine from newborn screening results when and how individuals with CPT II may present and what their optimal treatment might be.

### P111. Changing Incidence of Disorders Included in Routine Bloodspot Screening in NSW

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Newborn blood spot screening has been offered to all babies born in Australia since 1964. The number of disorders has increased over the years, initially testing only for phenylketonuria and now more than 50 inborn errors are included. Evaluation of the efficacy of screening programs includes assessment of the incidence in the screened population. In order to assess any changes in observed incidences a review was conducted of each disorder included in routine bloodspot screening in NSW and ACT, from 1999 to 2018. The annual birth rate of the nearly 2 million babies increased from 91,204 to 105,001. For some disorders, despite ariation from year to year, no trend was observed over longer periods – for example, hyperphenylalaninemia varied with an annual observed incidence from 1:5700 to 1:33974 – but overall 1:9480. Similarly MCAD, the most common fatty acid oxidation defect, had no cases detected in 1998 but incidence over any 5 year period was around 1:14000. Some disorders trended. Primary congenital hypothyroidism varied from 1:3637 to 1:1324 more recently. This may reflect changing practice on who to treat plus modifications in maternal diet exposing the foetus to lower iodine. Cystic fibrosis varied from 1:2357 to 1:3518 more recently. This could reflect reproductive choices of families. The numbers are not sufficient to detect changes in the other rarer disorders with an incidence of <1:100,000. Despite significant short-term variation in observed incidence of the disorders included in routine newborn bloodspot screening most have remained consistent except where definition on who to treat has changed.

### P112. PKU Service Benchmarking Following Implementation of the Australasian Consensus Guidelines: A Single Site Audit

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**Background:** The Australasian consensus guidelines for the management of phenylketonuria throughout the lifespan were endorsed by ASIEM in September 2017. The guidelines provide metabolic clinics with evidence-based recommendations to inform best practice and promote optimal outcomes for individuals with PKU. **Aim:** To benchmark our PKU service clinical practice against the Australasian consensus guidelines using repeated audits at 12 month intervals to measure outcomes overtime. **Methods:** Four recommendations from the consensus guidelines relevant to dietetic management were selected for audit on a yearly basis; (1) Full diet assessment, (2) Nutritional pathology performed, (3) A minimum of four Phe samples collected, and (4) At least two Phe results <800 umol/L. Data were collected from attendance records and pathology results maintained on electronic medical records. The baseline audit occurred in July 2018. A follow up audit is scheduled for July 2019 to compare results overtime. **Results:** The baseline audit showed that yearly diet assessment was completed in 92% of our patients and 46% had a nutritional pathology performed. Over half (58%) had a minimum of four Phe samples collected and 61% of patients had at least two documented Phe results <800 umol/L. The four selected guideline recommendations were all achieved by only 25% of our adult patients with PKU. Data for the second audit are currently being collected. **Conclusion:** We anticipate that the endorsement of Australasian consensus guidelines will improved clinical care of patients with PKU assessing our service which will be reflected by an alignment towards best practice recommendations overtime.

### P113. Impact of Population Screening on Australian Genetic Services

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**Background:** Current practice within Australian Genetic Services is for reproductive carrier screening to be offered in the presence of family history of an autosomal recessive condition. We sought to determine how Australian Genetic Services are currently approaching pre-pregnancy carrier screening as well as genetic health professionals' views towards the imminent shift from family history based reproductive carrier testing to a population screening approach. **Method:** Genetic health professionals were invited to participate in a work-force analysis survey comprised of questions exploring the current approach to pre-pregnancy carrier screening and the attitudes towards screening on a population level. **Results:** 57 surveys have been returned. Approximately two-thirds of the participants are genetic counselors ( $n = 38, 67\%$ ), and almost one-half of participants had over 10 years' experience within the field of genetics

( $n = 27, 48\%$ ). Of the 79% ( $n = 45$ ) of participants who reported that their service currently offers pre-pregnancy carrier screening, half reported that this testing is offered regardless of family history presence ( $n = 22, 49\%$ ). Of these, under a third ( $n = 6, 27\%$ ) reported that the testing was paid for by the service. 89% of participants believed that pre-pregnancy carrier screening should be a routine part of pre-pregnancy work up although only 5% felt that genetics services are in a position to fully implement the screening on a population level. 60% of participants felt that prepregnancy carrier screening raised issues of health inequality in relation to reproductive options. **Discussion:** Qualitative analysis of exploratory questions in the survey will contribute further to the findings.

### P114. Multi-site Investigation of Rapid Genomic Testing in Acutely Unwell Children in Australia: Learning from Implementation

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Clinical genomic testing holds the potential to influence the care of acutely unwell children with genetic conditions, accelerating diagnosis and guiding management in real time, particularly when performed with rapid turnaround times. We undertook a multi-site rapid genomic testing project in Australia and, using implementation science principles, identified lessons to guide future service development and policy. **Aim/Methods:** To identify multi-site barriers and enablers to implementation of rapid clinical genomic testing for acutely unwell children. We gathered data from: (1) Observations of project working group meetings ( $N = 7$ ), January 2018–June 2019; barriers and enablers to implementation were discussed by clinical and laboratory staff from multiple sites, and 2. Interviews with key operational/clinical/laboratory staff ( $N = 63$ ), invited to interview between April 2019 and June 2019. To date, 12 interviews have been undertaken with the rest scheduled. Data were analyzed deductively (Consolidated Framework for Implementation Research, CIFR) and inductively (thematically). **Results/Discussion/Conclusion:** All five CFIR domains (Intervention Characteristics, Outer Setting, Inner Setting, Characteristics of Individuals and Process) were represented in the data. The observations highlighted shifting priorities, from an early emphasis on the Intervention Characteristics to Process. The interviews showed that the implementation climate (Inner Setting) and personal attributes (Characteristics of Individuals) were key to implementation outcomes. Emergent themes include leadership, communication, the role of informal education, and enthusiasm/sustainability. Identifying and applying learnings from early implementation projects is essential to facilitate future sustainable scaling-up. The changing emphasis on priorities for rapid clinical genomic testing, dependent on implementation stage, indicates that a flexible, iterative approach to implementation will be needed for future clinical applications.

**P115. Withdrawn****P116. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity**

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Breast cancer (BC) comprises multiple distinct subtypes that differ genetically, pathologically, and clinically. Here, we describe a robust protocol for long-term culturing of human mammary epithelial organoids. Using this protocol, >100 primary and metastatic BC organoid lines were generated, broadly recapitulating the diversity of the disease. BC organoid morphologies typically matched the histopathology, hormone receptor status, and HER2 status of the original tumor. DNA copy number variations as well as sequence changes were consistent within tumor-organoid pairs and largely retained even after extended passaging. BC organoids furthermore populated all major gene-expression-based classification groups and allowed *in vitro* drug screens that were consistent with *in vivo* xeno-transplantations and patient response. This study describes a representative collection of well-characterized BC organoids available for cancer research and drug development, as well as a strategy to assess *in vitro* drug response in a personalized fashion.

**P117. The Epileptology of GNB5 Encephalopathy**

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**Background:** GNB5 encodes guanine nucleotide-binding protein subunit beta-5 (Gβ5). Gβ5 assists in the downregulation of central nervous system G protein signalling. Pathogenic variants in GNB5 cause an autosomal recessive neurodevelopmental disorder with neonatal sinus bradycardia. Seizures or epilepsy occurred in 10/22 previously-reported cases, but the description was limited. A genotype-phenotype correlation has been reported, with truncating variants causing a severe neurodevelopmental outcome, and missense variants resulting in a milder phenotype. **Aim:** To delineate the epileptology of GNB5 encephalopathy. **Methods:** Two individuals were identified in a New Zealand cohort of developmental and epileptic encephalopathies (DEEs). The literature and GeneMatcher were searched for additional cases. Clinical and molecular data were obtained for each patient. **Results:** Nine patients, including five new patients, were identified. 4/7 families were consanguineous. Epileptic spasms were the most frequent seizure type, occurring in 8/9 patients, and began at a median age of 3 months. Focal seizures preceded spasms in three children. Three children had burst-suppression on EEG, three hypsarrhythmia and one evolved from burst suppression to hypsarrhythmia. MRI showed cerebral atrophy in one child and cerebellar atrophy in another. All nine had abnormal development prior to seizure onset and ultimately had profound impairment without regression. Hypotonia was present, with contractures developing in two older patients. Eight had documented bradycardia. All nine had biallelic truncating variants. **Discussion:** Children with GNB5-DEE have developmental delay from early infancy and an epileptic encephalopathy characterized by epileptic spasms. Genotype-phenotype correlations are emerging as larger numbers of patients are recognized.

**P118. Solving the Phenotype-Genotype Dilemma: HBA MLPA Reveals Novel Deletions in Two Families**

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Alpha thalassemia is caused absent or impaired production of the alpha globin chains of hemoglobin. The most common genetic variants causing this condition are by deletions affecting one or more alpha globin genes, *HBA1* and *HBA2*, on chromosome 16p. The clinical manifestations of this condition correlate with the number of alpha globin genes deleted. In hemoglobin H disease three of the usual four

copies of the alpha globin genes are deleted. Gap-PCR is frequently used to identify the common deletion variants causing this condition. A limitation of this method is that it only targets the common variants meaning that alternative analysis must be employed to detect variants in some patients. We present two cases in which the proband presented with Hemoglobin H disease, however this phenotype was not explained by the genotype identified by Gap-PCR and HBA gene sequencing. Performing multiplex ligation probe amplification (MLPA) allowed identification of the variants present in these families. These findings have promoted us to adopt this technique as a first line test for alpha thalassemia deletion analysis. MLPA offers a viable alternative method for identifying HBA gene copy number variants and may be helpful in identifying novel or alternative deletion not identified by Gap-PCR.

### **P119. GeneXpert Ultra for Quantitative BCR-ABL1 Testing – Thinking Outside the (Black) Box**

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The GeneXpert Ultra (GXU) assay (Cepheid) is a semi-automated system for the quantitation of BCR-ABL1 transcripts in the peripheral blood of patients with chronic myeloid leukemia (CML). Presence and levels of BCR-ABL1 transcript are confirmed at diagnosis and regularly monitored following tyrosine kinase inhibitor treatment. Introduction of this test to our laboratory in February 2018 was welcomed as a ‘laboratory dream’ for the molecular analysis of the almost 200 CML patients we routinely monitor. The biggest advantage has been the huge reduction in hands-on laboratory and analysis time, with single piece flow of samples reducing the turnaround time from up to 2 weeks to just 1 day. However, the GXU assay is not the ‘be-all-and-end-all’ of BCR-ABL1 testing. Despite its benefits it has limitations that must be considered with every sample tested. Of these, the major limitation is the detection of only the two most common BCR-ABL1 transcripts in CML – b2a2 (e13a2) and b3a2 (e14a2). Other transcript types do occur, and diagnosis and monitoring of these patients must rely on other techniques such as FISH, RT-PCR and ddPCR. Other drawbacks of the GXU assay include the lack of identification of BCR-ABL1 transcript type, return of invalid results for samples with high leucocyte counts and the reporting of quantitative BCR-ABL1 values below the assay’s documented Limit of Quantitation. It has become increasingly clear that despite being a ‘black box’ technology, the GXU assay still requires appropriate scientific input to ensure the clinical question relevant to each patient is correctly addressed.

### **P120. Data Provenance Check: A Cost-Effective Solution to Prevent Incorrect Diagnoses**

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**Background:** Ensuring provenance of genomics data is a critical quality check to avoid incorrect diagnoses. There are three main types of pre-analytical errors that could lead to the wrong diagnosis: sample mix-ups, sample cross-contaminations and incorrect kinship assumptions. **Aim:** To implement a cost-effective and automated NGS Data Provenance (NDP) check that facilitates early detection of pre-analytical error to minimize the risk of incorrect diagnoses.

**Methods:** Microarray and exome data of samples with previously identified issues were analyzed for sample mix-ups, cross-contamination and kinship issues using the NDP check. **Results:** All previous issues were identified. Moreover, the NDP check revealed further relevant information. In one case, a maternal sample from a trio was detected to be contaminated with the paternal sample, obstructing the identification of recessive variants. A second case was proven to be non-paternity, causing a high number of false positive de novo variants. In a third case, a sample mix-up was detected between two samples from the same batch. Finally, low levels of cross-contamination were detected among several unrelated samples from the same sample preparation batch. **Conclusion:** We have implemented an automated framework for early identification of pre-analytical errors. Sample mix-ups, kinship and cross-contamination checks, including maternal cell contamination, were consolidated from multiple existing assays into one automated and cost-effective solution that moves pre-analytical error detection from a reactive to a proactive approach.

### **P121. Pilot Study: Exploring the Role of Genetic and Community Support Services in Supporting Mental Health**

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**Background:** Australia is committed to patient centred care (PCC), which focusses on ‘the whole person’, through the Australian Charter of Health Care Rights (2007) and the Australian Safety and Quality Framework for Health Service Standards (2011). Engagement with the genetic health system through preparing for testing, testing, diagnosis, communication, treatment and management can cause higher levels of anxiety as evidenced by many existing and recent studies. **Aim:** This pilot study aimed to investigate the perspectives of genetic health professionals and support services regarding their capacity to support patients’ mental health. **Method:** Semi structured interviews were carried out with genetic counselors, clinical geneticists and support services leaders. Interviews were transcribed and thematically analyzed. **Results:** 7 participants were interviewed including 3 genetic counselors, 1 clinical geneticist and 3 support group leaders. The main themes were: mental health issues identified by health professionals differ from those identified by support group leaders; peer support services do not feel equipped to deal with severe mental health concerns and are of the belief that individuals and families are often not receiving appropriate support for mental health when they engage with support services; health professionals have mixed feelings regarding whether identifying mental health issues is within the scope of their role, however believe they should be referring patients on. **Conclusion:** This study shows that both health professionals and support services are aware that patients are not receiving the appropriate level of mental health support. Further research is needed.

### **P122. Lab Tests Online Australia – A Key Partner in Increasing Genetic Test Literacy**

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Consumer health literacy is essential to ensuring that the Australasian public are empowered as partners in their healthcare, and

understanding diagnostic pathology such as genetic tests, is integral to that goal. Lab Tests Online Australia (LTOAU) is an internet-based education resource directed at health consumers delivering independent, authoritative information managed and written by practicing pathologists and scientists. The goal is to support both consumers and clinicians and is careful to not provide direct clinical advice. The LTOAU content includes general information on genetics and more detailed resources for a range of genetic tests that are reimbursed on the MBS with the goal of including information on the site for all such tests. There has been a 43% increase in web site activity in the past year, totaling 2.1 million visits and there have been over 94,000 visitors to parts of the site related to genetics tests. Text based information on genetics has been supplemented by several videos. With both more visitors to the site and the introduction of more genetic tests into routine practice we anticipate the need for more consumer orientated information about genetics. To that end we are keen to recruit more scientists, pathologists and genetic counselors as HGSA members who can contribute such information to LTOAU. As Australia moves into a new era of direct access to pathology results, LTOAU is ideally placed to provide high quality information and as a resource to better meet the needs of health consumers.

### **P123. Telling Families Unexpectedly About Clinically Actionable Genetic Information: EXAMINING the Psychosocial Implications and Clinical Outcomes**

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Up to 11,000 Australian women diagnosed with high-grade non-mucinous epithelial ovarian cancer in the last 15 years were not offered germline BRCA1/2 testing. TRACEBACK aims to redress this by retrospectively testing tissue from women with a history of ovarian cancer who missed the opportunity for testing, including testing DNA from surgical blocks of deceased women with a waiver of consent. If detected, women, or their next-of-kin, will be notified by TRACEBACK of the existence of a mutation in a clinically actionable ovarian cancer susceptibility gene. TRACEBACK.E aims to evaluate the effectiveness of TRACEBACK by examining the psychosocial implications for families receiving this genetic information unexpectedly, the dissemination of this information to at-risk family members, and their uptake of genetic testing and cancer risk management strategies. TRACEBACK.E takes a mixed-method approach using qualitative interviews and a prospective, longitudinal survey. We will conduct interviews with participants (~60) at baseline, when the receipt of the genetic information will be recent, enabling an in-depth exploration of this time-point. We will analyze the qualitative data thematically using a hybrid (deductive and inductive) approach. The survey will capture clinical outcomes of TRACEBACK (e.g., cascade testing), decision-making, family communication, satisfaction with the TRACEBACK process, and psychosocial adaptation to the genetic information. Data will be collected upon recruitment to TRACEBACK.E (baseline), then at 6-monthly intervals over 24-months, enabling analysis of psychosocial changes over time. The findings from this study will be critical to measuring the success of TRACEBACK and the potential to translate TRACEBACK to other tumor streams.

### **P124. 'The Benefit That Comes from My Existence': Patients' Experiences of Consenting to a Cancer Rapid Autopsy Program**

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CASCADE, an Australian-first cancer rapid autopsy program, was established in 2012 to enable functional and genomic analyses on metastatic tissue. Patients with metastatic disease are recruited to CASCADE when they have no further curative treatment options available. Little is known about patients' experiences of consenting to a rapid autopsy at the end-of-life, and the implications of consenting to this unique research program. This study aims to explore patients' experiences of consenting to CASCADE, and the personal and familial implications of this decision. Using a qualitative approach, we conducted interviews with CASCADE patients. Recruitment for interviews is ongoing and is mediated by clinicians who recruit for CASCADE. We used thematic analysis, coding interview transcripts inductively and independently, then compared coding to identify themes, concepts, and ideas, to generate the findings. To date, 10 interviews have been conducted with patients who have consented to CASCADE. Most had agreed to participate with little deliberation: their decisions were based on altruism and a wish to benefit others, a desire to reciprocate for the care they had received, and an unfulfillable aspiration to donate their organs. Consenting to CASCADE created a space during end-of-life to discuss death with their support network but otherwise minimally impacted their everyday living. Patients expected that their families would respect their wishes and agency. Despite this, some patients had not disclosed enrolment in CASCADE to their parents to minimize distress. These findings suggest that discussions about rapid autopsy were acceptable to our participants and consenting offers meaning during the end-of-life.

### **P125. Establishment of an Asia-Pacific Dried Blood Spot External Quality Assurance Program**

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*Introduction:* An expansion in laboratories using dried blood spots (DBS) for newborn screening and chronic condition monitoring, combined with limited availability of Centres for Disease Control DBS external quality assurance (EQA) material for non-US

participants and quarantine regulations, prompted the development of an Asia-Pacific DBS-EQA program. The Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP), in conjunction with the Sweat Testing Advisory Committee, present results for the 2019 pilot DBS-EQA program. *Methods:* The DBS program material is prepared from blood spiked with analytes at six linearly related levels. Each level is provided in duplicate as a set of twelve DBS samples sent as one shipment annually to enrolled participants. Initial analytes are thyroid stimulating hormone (TSH), immunoreactive trypsinogen (IRT), tyrosine (tyr), phenylalanine (phe) and 17 hydroxy progesterone (17OHP). Initial analytical performance specifications (APS) were established as  $\pm 10\%$ , with all-laboratory median used as the measure of central tendency. Participant results are compared for imprecision, bias and linearity using standard RCPAQAP reporting. *Results:* Five Australasian laboratories enrolled for the first cycle of this program. The initial results demonstrated linearity within and between laboratories for TSH (1.0–350 mIU/L), IRT (8–220 ug/L), phe (20–2020 ug/L), tyr (35–1600 ug/L) and 17OHP (5.0–150 nmol/L). Bias was assessed and  $>80\%$  of laboratories were within the APS for TSH, IRT, phe and tyr, confirming the validity of these performance limits. *Conclusions:* We have successfully established a DBS-EQA program for the Asia-Pacific region that fulfils an emerging local need and opportunity for harmonization. Future developments include analyte expansion and clinical case interpretation.

### **P126. Consent as a ‘Cure-All’? The Role of Consent in Genetic Data Sharing and Secondary Use**

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Consent is often discussed as being central to data protection regulation. Consequently, concern over legal roadblocks to genetic data sharing has motivated projects to revamp consent. These efforts are complicated because genomic medicine sits uneasily between research and clinical care. Consent tends to be seen as a ‘cure-all’ to enable broad genetic data sharing. However, this paper explores the extent to which consent is, and should be, a legal requirement for secondary use of genetic data in Australia. First, we show that the various information privacy laws say little about what consent should look like. Second, we show that there are lawful ways to use and share health information for secondary purposes without consent. For example, research exemptions attempt to balance competing public interests. Another exemption based on ‘reasonable expectations’ could be used to reflect social norms such as altruism. However, relying on these exemptions might be practically difficult. One solution may be to tweak them or to add new exemptions. Another could be to harmonise state and federal laws, to also settle confusion around transborder data sharing between unrelated entities. While data sharing is not as obstructed as people might think, we need a regulatory approach that is relevant to the different applications of genomic medicine and readily accessible to non-lawyers. Recognizing the limitations of clinical and research paradigms, this regime could be based on a public health framework. This would refocus attention towards beneficial outcomes of data sharing and avoid stretching consent beyond its ethical and legal limits.

### **P127. Use of a Diagnostic DSD Gene Panel and Implications for Clinical Care**

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The individualized clinical care of DSD can be complex and must consider patient rights, parental rights, and medical evidence. The Reproductive Development laboratory at the Murdoch Children’s Research Institute (MCRI) has been working to understand the genetic mechanisms underlying sex determination and DSD. This has included the creation and validation of a targeted gene sequencing panel specific to DSD. This research panel provided a quick and effective method to improve genetic diagnosis rates from 13% to around 40%. In 2018, Victorian Clinical Genetic Services (VCGS) adopted this DSD gene panel, and it is now routinely applied as a clinical tool to assist the diagnosis of individuals with a range of DSDs. In the first year of its availability, the DSD gene panel has been accessed by 35 patients nationally. In a number of cases, a genetic finding has transformed clinical practice for individuals. A diagnosis has enabled clinicians to provide individuals and their families a better understanding of the condition’s natural history and to empower families to participate in health care decisions. Genetic counseling in cases where there may be implications for other family members or future children is also made possible. We will present three cases that illustrate how a genetic diagnosis such as a pathogenic variant in the SRD5A2, MAP3K1 or NR5A1 gene informs clinical care. The multi-disciplinary team uses this genetic information to predict malignancy risk and future gonadal function. Outcomes also include developing personalized psychosocial supports for families and patients.

### **P128. The Practice of Engaging Aboriginal and Torres Strait Islander Communities in Genome Research**

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Australia’s National Health Genomics Policy Framework recognizes the obligation to ensure that Aboriginal people and Torres Strait Islanders (Australia’s First Peoples) are at the forefront of developments in precision medicine and the broader integration of genomics onto the healthcare system. Indigenous inclusion in this area has requirements that go beyond general principles for Indigenous health research. This need exists for historical reasons and to maintain an enduring connection between patients, participants and communities and their contribution to the biospecimens and data that underpin genomics. The National Centre for Indigenous Genomics (NCIG) has developed a framework that addresses these requirements through strong Indigenous governance, enduring community engagement with stored material and genomic data, and rigorous data management systems. We present an Indigenous perspective on the community engagement component of this framework, describing the practical application of ‘doing the right thing’; proceeding at ‘the pace of trust’; obtaining informed

consent as part of an enduring relationship; acknowledging cultural perspectives; understanding the diversity of views and practices within and between communities; respecting the need for community ownership and enabling community involvement in research. This Indigenous methodology for community engagement has been developed through action research involving communities participating directly in genomic research. In combination with NCIG's Indigenous governance and data management systems, it provides a model for Aboriginal people and Torres Strait Islanders to play a leading role in the future development of genome science and precision medicine in Australia.

### **P129. Telomere Length in Skeletal Muscle and Leukocytes, and Aerobic Fitness**

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**Background:** Telomeres shorten due a lack of telomerase activity and progressive cellular replication. As such, telomere length (TL) is indicative of cellular replicative reserve and biological age. Current evidence indicates TL is associated with healthy living and suggests that a higher aerobic fitness is associated with longer telomeres. **Aims:** The aim of this study was to investigate the relationship between TL in a minimally proliferative tissue (skeletal muscle) and a highly proliferative tissue (leukocytes). Second, to explore the relationship between TL and markers of aerobic fitness in both tissues. **Methods:** We measured TL (T/S ratio) in leukocytes and skeletal muscle from 82 recreationally active healthy men (age = 31.4 ± 8.2; BMI = 25.3 ± 3.3) from the Gene Skeletal Muscle Adaptive Response to Training study. Using an integrated fitness score (Watt peak, lactate threshold, and citrate synthase activity), we ran robust linear models to examine if TL was associated with aerobic fitness scores or chronological age. **Results:** Telomeres were longer in skeletal muscle than in the leukocytes ( $p < .001$ , 95% CI [0.33, 0.45]). TL in skeletal muscle and leukocytes were correlated ( $r^2 = .35$ ,  $p = .002$ ). Aerobic fitness was not correlated with TL in skeletal muscle ( $r^2 = 0.006$ ,  $p = .8$ ) or leukocytes ( $r^2 = -.006$ ,  $p = .8$ ) even after adjusting for age (skeletal muscle  $p = .8$ ; leukocytes,  $p = .7$ ). **Discussion:** These data suggest that aerobic fitness is not associated with TL in blood or skeletal muscle at least in a recreationally active, younger cohort of men (18–45 years of age). The moderate correlation indicates synchrony in the length of telomeres between highly and minimally proliferative tissue.

### **P130. Development of a Framework to Include Indigenous Australians in Training Pathways for Genetic Counselors**

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Indigenous Australians are under-represented in genetic health employment settings and genetic counseling clinical services. Increasing the number of Indigenous practitioners would enhance services' provision of culturally responsive care and support self-determination for Indigenous communities in genetic health. To date, no Indigenous students have ever enrolled in the Master of

Genetic Counselling (MGC) at The University of Melbourne (UOM). Educational institutions, with responsibility for training genetic health practitioners, are faced with specific challenges in recruiting Indigenous students and supporting their successful transition into the workforce. Broadly, these challenges are twofold: the cultural relevance of existing genetic health curricula, and the educational disadvantage of Indigenous students and impediments faced in accessing and completing tertiary education. The Victorian Government Department of Health and Human Services have funded a project to encourage and facilitate Indigenous engagement in the genetic counseling training pathway at UOM. The project will address the range of barriers that hinder Indigenous students' participation in the requisite degree program, subsequent professional employment and certification processes necessary to become a certified genetic counselor. This presentation will describe the intervention and evaluation strategy that has been developed to: (1) address academic entry barriers by addition of a preparatory year for the MGC program at UOM; (2) address financial barriers with a scholarship program to enhance the existing equity-based ABSTUDY program; (3) address employment transition barriers with a supported graduate training post and supervision to facilitate full certification as a genetic counselor with the Human Genetics Society of Australasia (HGSA).

### **P131. Early-Career Doctor Recommendations for Competencies in Genomics**

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**Introduction:** The skills required by early career doctors to competently engage with genomic medicine may be rapidly changing due to advances in genomic science and increased public awareness of genomic testing. To assist with the development of fit-for-purpose curricula in medical genomics, we explored the opinions of early career doctors about current knowledge and skill requirements for medical genomics. **Methods:** 15 early career doctors (1–6 years post-graduate) and 3 general practitioners in Wellington, New Zealand were interviewed. Interviews were transcribed and analyzed by inductive and deductive thematic analysis. Emerging themes were identified, grouped to form broader categories, then reanalyzed and further defined. **Results:** Interviewees thought there was a limited role for general doctors in clinical genomics. They identified their main roles as being to identify patients with genetic disorders and refer appropriately, and to explain genetic disorders to affected people. They recommended a genomic curriculum be immediately relevant to day-to-day practice, focusing on genetic and genomic consultation skills (communication to support patient perspectives; patient education; family history taking), information management, clinically applicable scientific knowledge (inheritance; patient identification), and cultural aspects of genetics and genomics. **Discussion:** Early career doctors have a traditional view of their role in genetics (detect-refer-educate) and suggested a curriculum to support this. They did not identify a change in the role based on the recent advances in pharmacogenomics and personal genomic testing. This information has utility for assisting with the development of fit-for-purpose undergraduate and postgraduate medical genetics curricula.

### P132. Auckland-Based Oncologists Perspectives on Genomics and Genomic Education Needs

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**Background:** Oncologists are at the forefront of the use of genomics in clinical practice as they must be literate in both germline predispositions to cancer and somatic mutations within the tumors being treated. The need for genomics education for oncologists has been well recognized globally. While international studies have examined education needs of oncologists, the New Zealand context is different because oncologists rarely have experience ordering germline genetic testing. New Zealand oncologists' genomic education needs have not been previously studied to our knowledge. **Aims:** The aims of this project were understanding New Zealand oncologists' perceptions of genomics and establishing their perceived educational needs. **Methods:** A diverse group of medical oncologists employed by Auckland District Health Board were identified through purposive and snowball sampling. Eleven qualitative semi-structured interviews were conducted and transcribed verbatim. Thematic analysis was used to identify important themes. **Results:** Preliminary data suggests oncologists view the current formal genomics training as insufficient. Participants suggested a multidisciplinary approach to ordering and interpreting genetic results. Limited funding for somatic testing and treatments is a barrier to clinical uptake of somatic testing. Participants suggested a variety of learning methods which could be implemented in the future. **Conclusions:** The use of genomics in clinical practice is changing for oncologists in New Zealand and further education is required. Support from genetic services and the development of closer working relationships may assist oncologist's understanding and use of genomics. Further research is required to gather the perspectives of oncologists working outside of Auckland.

### P133. An Economic-Modelling Framework to Assess the Impact of Population-Wide Preconception Carrier Screening for Genetic Disease

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**Background:** Children with genetic disease (GD) incur substantial costs to the family and healthcare system due to the chronic and early-onset nature of the GD. Preconception carrier screening (PCS) offers the possibility of averting GDs by identifying at-risk couples and enable them to make reproductive choices (e.g. preimplantation genetic diagnosis). This could potentially reduce healthcare utilization and cost attributed to GDs and improve the life of that child and their family. **Aim:** We describe a modeling framework of an ongoing study that aims to assess health and economic impact and the cost-effectiveness of offering population-wide PCS for GD to inform public funding decision. **Method:** A simulation model is constructed using the 2016 Australian Census as the base population and then applies a series of probabilities (e.g. carrier rate, incidence of babies with GD) and costs (e.g., cost of PCS, genetic counseling, diagnostic and follow-up) sourced from published data. Sensitivity analysis is conducted to address uncertainty. Key assumptions and limitations (e.g., paucity of data to inform the model) are discussed. The impact of population-wide PCS is

measured by reduction of GD cases, number of unaffected babies and averted lifetime cost of care. The cost-effectiveness is measured using incremental-cost (e.g. cost of PCS, confirmatory testing, counseling) per quality-adjusted-life-years gained from GD prevented. Examples of the impact of PCS and the different reproductive decisions of at-risk couples will be illustrated. **Discussion/Conclusion:** Population-wide PCS holds significant promise in providing societal gains by averting affected pregnancy and reducing economic burden associated with having a GD.

### P134. Survey of Public Opinions about Sharing Genomic Data from Medical Records with Researchers

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Queensland Health (QH) is making a significant investment to introduce genomic testing to the public health system. As QH becomes a repository for patient genomic data, requests to share this data with researchers will increase. However, sharing of genomic data comes with a unique set of ethical, legal and social considerations. This project aimed to understand public opinions about the genomic data contained in medical records being used for research purposes to inform public policy and discussions around genomic data sharing. From February to April 2019, members of the public completed a written questionnaire that ask their opinion and concerns about genomic data stored in medical records being shared by QH for use in research. A total of 1661 people participated in the survey. Most participants wanted to be given the choice to have their genomics data from medical records used in research. Their expectations of how often they needed to be approached for permission for genomic data use depended on whether the genomic data was identifiable or anonymous. Participants were most concerned with genomics data sharing resulting in; discrimination (insurance and employment), data being used for marketing, and genomic data being made publically available. Given the sensitive nature of genomics data ensuring that genomic data sharing and management practices in the public health system reflect public expectations is an important consideration to maintain trust. The findings from this survey are an important starting point to inform discussions about the management of genomics data sharing held within Queensland's health system.

### P135. From Theory TO Practice: The Evolution of Mainstream Genetic Testing for Patients with Breast Cancer

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'Mainstream' genetic testing represents a change in clinical practice towards non-genetic specialists facilitating genetic testing, and results interpretation with their patients to inform decisions around treatment and ongoing care. Further, the introduction of specialist facilitated MBS funded testing has increased the number of patients accessing genetic testing as part of routine oncology care, and external to a genetics clinic. We sought to develop a collaborative model of care between oncology services and the Parkville Familial Cancer Centre (PFCC) to deliver a mainstream genetic testing program. Oncology services registered with the program receive education and support from the PFCC in discussing genetic testing with patients, and a shared approach to results disclosure. Since the program's implementation in

2017, 175 patients have been tested, and 111 specialists have been trained across 8 oncology services. Analysis of our clinical data has identified a number of areas for protocol review including maintenance of trained oncology specialists, interpretation of results and relevance of results to subsequent treatment decisions. We will present the benefits and challenges of delivering a mainstream genetic testing program to oncology clinics, and potential strategies to improve the program and maintain a 'gold' standard of clinical practice for patients accessing genetic testing.

### P136. Genomics in Clinical Care: Preparing Non-genetic Health Professionals

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Genomics has potential to impact almost all areas of medical care, however most non-genetic medical specialists lack confidence to order and interpret genomic tests. Melbourne Genomics has an upskilling strategy to meet education needs of practising non-genetic medical professionals: (1) internships; (2) blended learning short courses in clinical genomics; (3) workshops. Here we describe the case-based, discipline-specific workshops and their outcomes. Clinical cases address discipline-specific learning objectives. Using a modified Interrupted Case Method (Herreid, 2005), an experienced clinician alternates between presenting case details and directed questioning to guide group discussion and address key learning points. Clinicians experienced in genomics facilitate small group discussions. Pre- and post-workshop surveys evaluate impact. To date 183 clinicians have attended 5 of 9 planned clinical workshops (cardiology, acute care, congenital deafness and two pediatric neurology). Participants range from medical students to senior consultants. 70% (80/117) of survey respondents already used genetic or genomic testing in their clinical role; however, 76% (89/117) have no formal genetics training. Experience is highest for ordering chromosome and single gene tests (57% and 54%, respectively) and lowest for exome/genome tests (average 32%; range 9–61% across specialties). Self-reporting 'Good confidence' increased for ability to identify the right test for a patient (21% to 45%) and ability to interpret a genomic test report (18% to 41%). Respondents rate case-based learning as the most beneficial aspect. Other strengths include, genomics introduction, targeted discussion groups, and dedicated facilitators with clinical genomics experience. Evaluation is informing development of other components of our upskilling program.

### P137. 'Balanced Translocation' or Not? A Prenatal Case of Lymphedema Distichiasis Syndrome

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Lymphedema distichiasis syndrome (LDS) is caused by mutations in the FOXC2 gene, located at 16q24.1. This case review presents a family with a known balanced translocation ( $t(16;22)(q24;q13.1)$ ) and a

family history of lymphedema. Diagnosis of LDS was made clinically while counseling a couple during the diagnosis of a hydropic fetus at 12 weeks gestation. This was the third pregnancy for the couple. All pregnancies were conceived naturally. The couple had amniocentesis in the first pregnancy and had a healthy female baby. The Tasmanian Clinical Genetics Service first learnt about the couple during their second pregnancy, which was terminated at 13 weeks following the diagnosis of several fetal anomalies including increased nuchal thickness and malformations of the kidneys and brain. It was expected that the abnormalities were due to an unbalanced translocation; however, the products of conception returned a normal chromosome microarray (a G-band karyotype was not done). In the third pregnancy, the couple had NIPT which was reported as low risk for a chromosome abnormality or unbalanced translocation. However, 12 week ultrasound showed a significantly hydropic fetus. Following the diagnosis of LDS in the father of the fetus, it became apparent that the fetal hydrops was a severe form of LDS presenting in utero. Amniocentesis confirmed the fetus carried the balanced translocation. Sadly, this pregnancy was also terminated due to progressive hydrops. This case demonstrates that a balanced translocation is not necessarily balanced, and that increased genetic knowledge and advanced reproductive technologies may not provide solutions for some families.

### P138. Genomic Confidence and Somatic Testing Ordering in Queensland Cancer Physicians

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**Background:** Clinical exome sequencing (WES) has recently been introduced in Queensland as an alternative to Sanger sequencing. Little is known about cancer physicians' beliefs regarding the utility of somatic profiling and physicians' perceived genomic confidence. **Aim:** To ascertain whether genomics confidence and beliefs regarding the value of genomic profiling are associated with somatic test ordering. **Methods:** We surveyed all cancer specialist in Queensland following the introduction of WES sequencing at one centre. A validated instrument assessed somatic testing ordering, the relative value of molecular profiling as compared to pathology, and genomic confidence. A cash incentive was included in 75% of mailed questionnaires. **Results:** 110 physicians participated (response 45%); over half were oncologists, and the remainder were surgeons, hematologists and pulmonologists. Cash incentive improved response ( $p < .0001$ ) and oncologists were more likely to respond ( $p = .008$ ). Each month, physicians saw an average of 99.7 unique patients and ordered 2.25 somatic tests. Physicians weighted tumor pathology more heavily than tumor molecular profile with one third reporting that molecular profiling factored little in treatment decisions. 46.7% of physicians reported little to no genomic confidence. Regression analysis showed oncologists had greater confidence in interpreting somatic results, as did physicians who ordered more somatic tests and individuals who valued molecular profiling in decision making ( $p < .05$  for all). **Conclusion:** Physicians order two somatic tests on 100 patients seen monthly. Almost half report low genomic confidence. Higher confidence was associated with greater somatic test ordering, being an oncologist and perceiving tumor profiling to be valuable in decision making.

### P139. Collaboration: A NGS Panel Benchmarking Study of Public, Private and Research Laboratories within Queensland, Australia

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The implementation of high quality, accessible & affordable genomic services into routine clinical health care is a major challenge facing many countries around the world. Queensland State Government funding has supported Queensland Genomics and associated laboratories in a world first benchmarking collaboration involving public health, private pathology and research organizations with the aim of reviewing capabilities and demonstrating through collaboration our clinical grade NGS services available. Five laboratories processed NIST gDNA control sample/s through targeted panels which varied from as small as a Cardio Panel (0.572 Mb) to as large as a Whole Exome (67.3 Mb). Sequencing was performed on both Illumina and Life Technology Instruments. Results were compared using an independent international benchmarking body. 198 genes over 3385 unique regions were identified as being shared across all participant panels. SNV sensitivity measured >97% for all laboratories and PPV at >99%. Average Read Depths for all samples was >87x. The results show high quality clinical data and demonstrated the successful collaboration between the different NATA accredited laboratories. As the use of Genomics in diagnosis increases, it is important to maximize economies of scale and avoid duplication of pre-existing resources, especially when the infrastructure can cost millions. By focusing on current levels and capacity, this will enable QLD to minimize duplication by focusing on new areas or gaps in QLD's current framework and expertise. This study, by highlighting current capabilities will help drive the future direction of Genomics in QLD.

### P140. Classification of Genetic Variants in Patients with Fabry Disease Enrolled in the Fabry Outcome Survey (FOS)

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**Background:** The Fabry Outcome Survey (FOS; sponsored by Shire, a Takeda company) was designed to collect natural history data, including genetic information, from patients with Fabry disease. **Aim:** Increasing reports of atypical Fabry phenotypes prompted this expert review of identifiable mutations recorded in FOS. **Methods:** Genetic data were available from 1602 (42.9%) of 3737

patients in FOS (data extracted August 2018). The most prevalent mutation was IVS4 + 919G>A, occurring in 240 (15.0%) patients, followed by N215S (9.9%), A143P (4.2%), A143T (3.7%), and D313Y (2.1%). Members of the FOS Steering Committee (SC) assigned a list of 219 mutations to pre-determined phenotype categories: 'classic,' 'late onset,' 'genetic variant of unknown significance' (GVUS), 'benign,' 'other,' or 'unknown.' **Results:** A total of 1533 classifications were made by 7 assessors. Overall classifications made (n [%]) were: 'classic,' 686 (44.7); 'late onset,' 215 (14.0); 'GVUS,' 99 (6.5); 'benign,' 13 (0.8); 'other,' 53 (3.5); 'unknown,' 467 (30.5). After excluding 'unknown' classifications, the majority (>70%) of assessors agreed with classifications of 96 of the 219 mutations; of these, most were classified as 'classic' (n = 91 mutations), 4 mutations were classified as 'late onset,' and 1 was classified as 'other.' Inter-rater agreements per classification using Fleiss kappa were low and specifically: 'classic,' 0.13; 'late onset,' -0.02; 'GVUS,' 0.01; 'benign,' 0.15; 'other,' -0.02; and 'unknown,' -0.04. Overall, the inter-rater agreement was 0.03. **Conclusion:** These findings demonstrate that Fabry disease diagnosis cannot rely on genetic information alone, and that consensus is needed on the identification of classic mutations.

### P141. Biallelic Loss-of-Function Mutations in CSGALNACT1 Cause a Skeletal Dysplasia with Advanced Bone Age

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Chondroitin sulfate (CS) is covalently attached to specific core proteins, and ubiquitously exists at the cell surface and in the extracellular matrix in the form of proteoglycans. CS plays roles in various biological processes such as cell proliferation, cell signaling, and tissue morphogenesis by interactions with numerous growth factors and morphogens. CSGALNACT1 encodes CS N-acetylgalactosaminyltransferase-1 (CSGalNAcT1) responsible for CS biosynthesis to form the CS-repeating disaccharide region, [glucuronic acid – N-acetylgalactosamine (GlcA-GalNAc)]. Recently we reported a patient with CSGALNACT1-deficiency and a mild skeletal dysplasia with advanced bone age in infancy (Vodopiutz, Mizumoto et al. Hum Mutat, 2017). Here, we report that two patients with skeletal dysplasia with advanced bone age in infancy have compound heterozygous mutation, c.1294G>T (p.Asp432Tyr), and an intragenic deletion that removes exon 4 in CSGALNACT1, and have a homozygous mutation c.791A>G (p.Asn264Ser). The clinical features of the patients were a spondyloepiphyseal dysplasia with advanced bone age and a recognizable facial gestalt. The recombinant mutant CSGalNAcT1 (p.Asn264Ser and p.Asp432Tyr) showed a marked reduction in GalNAc-transferase activity compared with that of wild-type CSGalNAcT1. Relative numbers of CS chains were significantly reduced in the patient cells compared to a control subject. These findings indicate that the decrease in the GalNAc activity caused by the CSGALNACT1 mutations results in defects in the biosynthesis of CS, and imply that CSGalNAcT1 and/or CS chains play important roles in skeletal development.

### P142. Genomic Identity and Family Challenges: A Case Study from a Changed Diagnosis After 20 Years

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**Introduction:** Genetic Alliance (GA) provides an information and peer referral service for people with rare genetic conditions. A family contacted GA for information regarding Condition B for their child following array testing, changing a clinical diagnosis received 20 years ago. **Background:** Initial diagnosis for Condition A was based on phenotypical presentation 17 months after birth. Microarray testing was conducted as an additional syndrome was suspected. Information concerning health information was overlaid by family impacts and identity concerns. **Findings:** This case is of significance with first, substantial psychological impact. The parents and siblings have been providing peer support and long established, highly involved members of Condition A Foundation. This has led to challenges to their identity and bio-citizenship, with feelings of estrangement from their 'Condition A Family'. Second, changed diagnosis has altered the treatment, health effects and life expectancy for the affected individual. Third, this has altered future life plans of the family, notably siblings. Fourth, Condition 2 is very rare and no support services currently exist, increasing feelings of isolation and belonging. **Conclusion:** The issues and resolution for family members will be relevant to life stage, requiring different interventions and psychological support. While a change of diagnosis is not uncommon in the rare disease community, a repeat of this scenario, with significant time intervals, is likely in the future. However, predictions of the possible incidence and predictive triggers is unknown. Genetic testing and analysis, even years after an initial diagnosis, may have significant impacts on the family unit.

### P143. Gaucher Disease (GD)-Specific Patient-Reported Outcome (PRO) Measures for Clinical Monitoring and for Clinical Trials

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Disease-specific patient-reported outcome (PRO) measures are fundamental to understanding the condition/mindset and disease-related expectations of patients with genetic disorders such as Gaucher disease (GD), a pan-ethnic lysosomal disorder, characterized by hepatosplenomegaly, thrombocytopenia, anemia, bruising and fatigue, and associated with risk of co-morbid disorders such as Parkinson's disease and some cancers. Here we report the development and refinement of a GD-specific PRO measure, which aims to offer quantitative and qualitative assessment of a more complete range of GD concerns as an impetus to dialogue, and of symptoms not assessed in generic Health-Related Quality of Life questionnaires. A GD-specific PRO questionnaire was developed with input from 75 patients and 10 parents of patients in Israel. A qualitative interview study assessed content validity in 33 patients in the US, France and Israel according to FDA standards. First, a concept elicitation exercise explored patient experience of symptoms and treatments; findings were used to assess conceptual coverage of the questionnaire. A cognitive debriefing exercise involved patients completing the questionnaire using a 'think aloud' process, and explored patients' understanding and

relevance of instructions, items, response scales, and recall period. Five expert clinicians and a patient advocate were engaged as advisors at key stages and helped inform modifications to the questionnaire. The questionnaire includes 15 questions with a 6-point Verbal Response Scale plus nine 0–10 Visual Analogue Scales (VAS) and is intended for routine patient monitoring; a shorter version was developed for use in clinical trials.

### P144. Biallelic Variants in EFEMP1 in a Man with a Pronounced Connective Tissue Phenotype

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Connective tissue disorders are a broad spectrum of diseases that affect multiple structures including skin, vasculature and joints. We present here an individual with signs of a severe connective tissue disorder including multiple and recurrent abdominal and thoracic hernia, myopia, hypermobile joints, scoliosis, and thin translucent skin. Routine genetic testing did not provide a diagnosis, therefore we utilized whole exome sequencing. Candidate variants were found in three genes; however, we prioritized a pair of compound heterozygous loss-of-function variants in EFEMP1 (NM\_001039348.3: c.320\_324delTGGCA and c.615T>A). EFEMP1 encodes fibulin-3, a member of the fibulin family of glycoproteins. This group of extracellular matrix proteins are important for the integrity of elastic tissues including dermis, retina, fascia and vasculature; and other family members are associated with connective tissue disorders. To our knowledge, loss-of-function of EFEMP1 has not been described in humans before, however the Efemp1 knockout mouse displays a remarkably similar phenotype to the affected individual. Others have shown that knockout of Efemp1 in the mouse results in multiple herniation events, pelvic organ prolapse and premature ageing due to the loss of elastic fibre integrity in the visceral fascia. Using qPCR, we showed that dermal fibroblasts from the affected individual express a negligible amount of EFEMP1 transcript, a significant reduction compared to control ( $p < .001$ ). We therefore conclude that loss of EFEMP1 function in this individual is the cause of a novel connective tissue disorder, and can perhaps explain similar cases in the literature.

### P145. Rare Health Professionals

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**Background:** In 2013 the Genetic and Rare Disease Network (GaRDN) undertook co-design discussions with members to understand the needs of patients living with genetic and rare disease. A clear area of need was being able to access health professionals with knowledge and experience in rare disease. Health professionals, researchers and patients can use the register to connect with health professionals that have listed the condition of interest in their profile. **Aim:** To meet the needs of people living with genetic and rare diseases by providing them and clinicians access to health professionals with specialized knowledge. **Method:** public health research using a ten question survey was designed highlighting special interests, clinic services, telehealth services and pediatric to adult transitional planning. The survey was sent to individual clinicians and researchers; tertiary hospitals Australia-wide; medical, nursing and allied health professional bodies; Health Networks and Universities. The survey uses a targeted approach to relevant professional bodies and snowballs from there.

**Results:** To date approximately 160 Australian and international health professionals and researchers are on the register, encompassing 34 research, clinical and non-clinical categories. Requests to join the register have been received from Brazil, New Zealand and the UK.

**Discussion:** The register enables identification of rare disease specialists. Expansion and awareness of the register can provide metropolitan, rural and regional clinicians' easy access to specialist advice that can help in the diagnosis, treatment and management of their rare disease patients. In future we hope this survey will integrate with global activities like the European Reference Networks.

#### **P146. Summer Internship for Indigenous Peoples in Genomics (SING) Australia: Developing Indigenous Genomics Leadership**

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As genomics increasingly contributes to many advances and approaches in health research, there have been renewed calls internationally for equity and diversity within genomics research. However, given past experiences with culturally disrespectful and unethical engagement and/or research, challenges remain for Indigenous inclusion and participation in genomics research. For example, there are few Indigenous scholars leading Indigenous genomics research initiatives. In 2019, we will launch a pilot program to provide training and empowerment to Indigenous peoples in Australia in the context of the future of Australian genomics. A key part of this program includes the establishment of a Summer internship for Indigenous peoples in Genomics (SING) workshop in Australia and its surrounding network. The week-long SING workshop aims to establish collaborations and programs that support and encourage Indigenous students to become leaders in Indigenous genomics. Intensive workshops hosted by Indigenous and non-Indigenous scholars provide an opportunity for Indigenous students, scientists and health care professionals (either practicing or in training) who may be interested in genomics to learn more about the field from an interdisciplinary team and perspectives. This dedicated program will provide opportunities to connect trainees with mentors and foster interest in and passion for Indigenous-led programs of genomic research and scholarship. The overall goal of the program is to create opportunities to empower emerging Indigenous scholars; to create a network of Indigenous Australians that can provide a voice on genomic research in the future; and to promote positive engagement and Indigenous-led collaborations with communities around Australia.

#### **P147. Life at the Coalface: A Clinical Trial Coordinator's Perspective**

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Navigating a clinical trial landscape is often challenging and fraught with perils and pitfalls. Our research group has 6 years' experience running clinical trials in the Achondroplasia patient population. This

paper outlines our experience as a leading clinical trials unit, and highlights the real-life, day to day obstacles a clinical trial coordinator faces. We hope that our experience acts as a guide to those wishing to run clinical trials to assist in identifying potential challenges and overcoming unexpected ones. This presentation outlines our recruitment and consenting process, the importance of identifying suitable families for clinical trials, and how developing relationships with these families is imperative to long term success. We highlight the need to understand each family and their dynamics and their approach to stressful situations and coping mechanisms. Understanding these factors gives our team the opportunity to link families together for support and think outside the box by utilizing resources such as play therapy or clown doctors to make the child's hospital experience more positive. Our experience has highlighted the pivotal balancing act a trial coordinator plays, being the link between sponsor, monitor and families. As trial coordinators, we work at the very cutting edge of translational research and are faced with their unexpected hurdles and logistic difficulties such as: missed procedures; IV access; and drug and supply shortages while attempting to minimize disruption to families' everyday lives.

#### **P148. Clinical Audit of Cancer Gene Panel Testing at The Royal Melbourne Hospital**

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In late 2016, panel based genetic testing via the Peter MacCallum Cancer Centre laboratory was introduced in the Parkville Familial Cancer Centre at The Royal Melbourne Hospital. Multigene panel tests were introduced as an alternative to iterative single gene tests, which proved to be slow, inefficient and expensive. The department now administers a total of 16 different panel tests for a range of hereditary cancer conditions with demonstrable underlying genetic causes using a series of evidence based clinical testing criteria. As a publicly funded institution, The Royal Melbourne Hospital needs to be both accountable and transparent in its use of public funding, and therefore the efficacy of the testing administered by the Hospital needs to be adequately substantiated and evidently cost-effective. This study will use a tailored database extraction to collect and collate panel testing data and results from 2016–2019. The aim is to determine if the mutation pickup rate using panel testing is sufficient enough to be cost-effective. This will in turn provide the translational benefit of identifying areas of improvement for panel testing or altering the testing criteria as required. Our clinical impression to date is that some tests may not be as effective as anticipated. Some tests yield a relatively low percentage of positive results, while others have a very high mutation pick-up rate. Results will be analyzed and discussed.

#### **P149. What EXACTly Do We Know About Functional Constraint on Genes Associated with End-Stage Kidney Failure?**

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Large-scale high-quality exome sequencing data have allowed for the interrogation of low-frequency variations and their predicted pathogenicity. The accuracy of identification is useful for appropriate

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

### P150. Variant Interpretation Training for the Genomics Era: A 5-Year Comprehensive Strategy Aiming Towards Professional Competencies

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Variant interpretation (VI) is crucial to genomic testing, yet there is a dearth of literature on the educational needs and career pathways for this. Melbourne Genomics has a multimodal educational approach to developing a genomic-competent diagnostic workforce. Applying adult learning theory, we developed a suite of training programs (germline and cancer), culminating in the delivery of >15,000 learning hours in VI over 5 years to Victorian, national and international health professionals. The programs include: workplace immersion experiences (48 day cross-laboratory trainees (CLT)); 1–2 day professional development workshops (PDW); and two Masters-level subjects. Program evaluation used mixed methods. The majority of CLTs (7/10) were unfamiliar with VI at commencement. Mid-point interviews identified barriers and facilitators of using immersion experiences to acquire and maintain competency, such as the need for an initial PDW. PDW participants ( $n = 374$ ) were medical scientists (36.1%), researchers/bioinformaticians/students (26.2%), clinical geneticists (16.8%), other medical (17.3%), genetic counselors (3.1%) and other allied health professionals (0.5%). Pre-post surveys (188/374) and case assessments were analyzed to determine

actual versus self-assessed capability within and across workshops over time. Average self-assessed understanding of VI increased by 38.4% and 88.7% of participants anticipated incorporating their learning into their professional role. Drawing on the immersion and workshop programs, Masters-level subjects (24 modules across six curricula; 44 students to date) were developed using Bloom's taxonomy to align learning outcomes with desired VI competencies; subject evaluation is ongoing. This work provides a basis for an educational framework and competencies in VI that could be applied across the genomic workforce.

### P151. Victorian Newborn Screening Expanded CFTR Mutation Panel (2007–2018)

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**Introduction:** Molecular testing for cystic fibrosis transmembrane conductance regulator (CFTR) mutations forms the second tier of the Victorian newborn bloodspot screening (NBS) program for Cystic Fibrosis (CF). Until 2007, CFTR mutation testing included p.F508del alone for infants with an elevated (>99%) immunoreactive trypsinogen (IRT). In 2007, the NBS service expanded the CFTR screening panel to twelve mutations. Here we aim to evaluate the utility of this expanded CFTR mutation panel. **Methods:** The CFTR mutation data was retrieved from our NBS database for babies screened for CF between 2007 and 2018 (inclusive). The data was interrogated for: patients identified as a carrier or with CF from p.F508del mutation testing only; compound heterozygotes; and frequency of the mutations detected in the expanded panel. Comparison of data and statistical evaluation was performed using Microsoft Excel. **Results:** Between 2007 and 2018, 1308 babies were identified from the expanded panel with at least one CFTR mutation. Of these, 135 (10.3%) of babies were identified as homozygous and 47 (3.6%) as compound heterozygous. At least one p.F508del mutation was identified in 1121 (85.7%) of babies. Of the 187 (14.3%) of babies without a p.F508del mutation, five mutations were identified with a frequency of >1%: p.G551D ( $n = 58$ , 4.4%); p.N1303K ( $n = 29$ , 2.2%); p.G542X ( $n = 18$ , 1.4%); c.489+1G>T ( $n = 15$ , 1.1%); and, c.3718-2477C>T (15, 1.1%). The other six mutations each had a frequency of <1%: p.W1282X ( $n = 13$ ), p.R553X ( $n = 13$ ), c.1585-1G>A ( $n = 11$ ), p.I507del ( $n = 8$ ), p.R560T ( $n = 4$ ), p.V520F ( $n = 3$ ). **Conclusions:** The study showed that 85% of babies identified through the second tier with CFTR mutations could have been detected by p.F508del mutation analysis alone, 96% detected using a six gene mutation panel.

### P152. Psychosocial Issues of Filipino Parents with a Child with Maple Syrup Urine Disease

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**Introduction:** Maple syrup urine disease (MSUD) is a common inborn error of metabolism diagnosed in the Philippines. A family

may experience stress, anxiety, sorrow or feelings of helplessness when a child is diagnosed to have a genetic disorder which can lead to chronic care and disability. An illness in a child affects not only the child, but the whole family as well. *Materials and Methods:* In-depth interviews using a semi-structured set of questions was done between the months of November 2015–March 2016. A total of 12 parents were interviewed. *Results:* The diagnosis of MSUD in a child is indeed a stressful event for the family. Parents experienced fear, confusion, and hurt, among other emotions. Having a child with MSUD had a negative impact on their families, especially in terms of financial burden, dietary restriction, and marital conflicts leading to separation. However, some parents reported positive effects such as increased confidence in one's abilities to care for the affected child and closer relationships among family members. *Conclusion:* The findings of this study reflect the complex issues and problems of families with a child affected by MSUD. It will help form policies and guidelines for genetic counseling of MSUD patients and their families in the Philippines to assist families in coping with the diagnosis and improve outcomes of affected children.

### P153. 'It's Not a Loss for Nothing': The Experiences of the CASCADE Rapid Autopsy Program Team

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CASCADE is an Australian-first cancer rapid autopsy program, facilitating genomic analysis of metastatic tissue. The program creates an inimitable situation not only for patients and their families, but the clinicians tasked with patient recruitment; the on-call researchers attending autopsies; and those working with autopsy-derived tissue. Capturing the experiences of the clinical and research team is important to evidence the practical, psychosocial, and ethical aspects generated by a rapid autopsy program. We conducted a qualitative study using semi-structured interviews with the CASCADE clinical and research team. We thematically analyzed transcript data to produce an in-depth understanding of participant experiences. We conducted interviews with nine clinicians and eleven researchers ( $n = 20$ ). All expressed passion for CASCADE and derived psychosocial and professional benefits from being members of the CASCADE group. However, they simultaneously described tactics to resolve dissonant feelings regarding their role. Positive patient responses to the program validated professional involvement, while strategic recruitment minimized the likelihood of causing distress to either party. Honouring the patient's wish to participate justified the 'confronting' nature of autopsy research. Those using autopsy-derived tissue grappled with the thrill of scientific discovery while acknowledging the circumstances of its collection. Ultimately participants upheld that the significance of the research, and what it means to end-of-life patients, outweighs any burdens. This research is the first to characterise how a rapid autopsy program team functions to maintain its success and address challenges resulting from its conduct. Findings may aid the current CASCADE team or researchers interested in developing a similar program.

### P154. Helping Culturally Diverse Populations Understand Genomics: Development and Evaluation of a Plain Language Resource

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*Background:* As genomic testing is increasingly incorporated into routine healthcare, it is crucial that the public are provided with reliable information to improve genetic literacy levels and inform decision making. It is imperative that these resources meet the needs of culturally and linguistically diverse (CALD) communities, who may face greater challenges in comprehending health information that is not presented in their first language. Currently there is a lack of culturally appropriate genomic resources available for these communities. *Aim:* To develop and evaluate a clinical genomic testing resource to assist CALD communities. *Methods:* The exploratory, sequential, mixed methods research design employed a survey followed by focus groups. The survey was completed by healthcare interpreters ( $n = 18$ ) from two hospitals in Melbourne during March 2019. Views were sought about the utility of genomic resources and interpreter satisfaction with patient understanding. Descriptive data analysis provided themes for the focus groups with individuals from CALD backgrounds due to be held in May 2019. Here we report on the findings from the survey. *Results:* Preliminary data from the survey indicated that healthcare interpreters were somewhat satisfied ( $n = 6$ ) that patients from CALD communities understand genomic information. The interpreters expressed concern about 'complicated information' and 'cultural differences' in consent and testing. Interpreters encouraged the use of 'simplified explanations' and 'easy to read' resources. *Conclusion:* This research is important in ensuring that CALD communities have a strong voice in the development of a genomic resource to help individuals better understand genomic testing and its implications.

### P155. Treating Muscle Weakness and Fatigue in Neurofibromatosis Type 1

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*Background:* Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder affecting 1:3000 individuals. The condition is associated with a high tumor burden, but cognitive issues and musculo-skeletal defects can have high impact on pediatric quality of life. Muscle weakness and fatigue is notable from early childhood, and ~30% of NF1 children report a low self-concept for physical abilities. While initially weakness and poor co-ordination were suspected to be neurological, preclinical models suggest an underlying metabolic myopathy. *Aim/hypothesis/research question:* We aimed to evaluate

the effectiveness of a variety of dietary interventions and nutritional supplements on intramyocellular lipid accumulation (IMCL) and muscle function in the limb-specific Nf1 knockout mouse model (Nf1Prx1<sup>-/-</sup>). L-carnitine and MCFAs will be compared alone and together; we will model cheat days with intermittent dose skipping; and test a common 'mitochondrial cocktail' containing L-carnitine, riboflavin and CoQ10. *Methods:* After 8 weeks of treatment in situ muscle physiology was performed to assess muscle force (mN), rate of fatigue over 120 contractions and recovery. Muscles were weighed (mg), sectioned and stained with H&E, Oil red O and BODIPY to examine fibrosis and intramyocellular lipid. *Results:* Nf1Prx1<sup>-/-</sup> mice treated with MCFA's + carnitine and mitochondrial cocktail show reduced muscle fatigue and increased recovery compared to normal chow fed Nf1Prx1<sup>-/-</sup> muscle. Additionally, all treatments reduced IMCL in muscle. *Discussion/Conclusion:* Recent advances in NF1 muscle research have resulted in a number of potential therapies and subsequently a clinical trial to treat muscle weakness and fatigue has begun in NF1 children.

### **P156. ACTA2 Mutations and Non-syndromic Thoracic Aortic Aneurysms/Dissections (TAAD)**

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*Background:* Mutations in ACTA2 (smooth muscle alpha-actin) are the most common monogenic cause of non-syndromic TAAD. Mutation carriers also have an increased risk of premature coronary artery disease and ischemic strokes, and histopathologic studies have supported the implication that ACTA2 mutations cause dysfunction in several vascular beds. We sought to characterise and document the phenotype in our population of ACTA2 mutation carriers, and to determine whether extensive vascular screening is indicated to detect silent vascular pathology in such patients. *Methods:* Phenotype review for patients harbouring ACTA2 mutations attending our clinic was conducted; these patients were members of one of two separate families. *Results:* From a total of 11 patients who underwent genetic testing, we identified 6 heterozygotes for ACTA2 mutations. These individuals are either probands, having the mutation identified through a Next Generation Sequencing Aortopathy panel, or mutation carriers detected through cascade/predictive testing. One suffered an aortic dissection at 45 years, and one underwent prophylactic aortic root replacement at 43 years for an aortic root diameter of 49 mm. Of the remaining 4 mutation carriers, the youngest (36 years) has normal aortic dimensions, while the remaining 3 have mild-moderate aneurysmal aortic root dilatation. None of our cohort have suffered premature vascular diseases in other vascular territories. *Conclusion:* ACTA2-mutation carriers in our cohort have a high prevalence of TAAD, but none of these individuals have suffered insults in other vascular beds. However, given the potentially life-threatening nature of acute vascular events, vascular screening may be useful in identifying vascular pathologies amenable to preventative therapy.

### **P157. Sample Quality Control Assessment of Long Read Sequencing and Low Input Libraries**

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Long-read sequencing and miniaturization of library preparations are becoming increasingly common as new next-generation

sequencing workflows are developed. Traditional quality control methods do not provide the required sizing accuracy of DNA greater than 50 kb or the sensitivity allowing for sample conservation during the quality control assessment steps. The Femto Pulse system by Agilent Technologies works to streamline quality control by separating genomic DNA up to 165 kb in as little as 70 min, down from the 16+ h required for traditional agarose PFGE. The unparalleled single cell gDNA sensitivity of the Femto Pulse allows for preparation of low input NGS libraries from cfDNA, RNA, and miniaturized traditional DNA NGS libraries. Quality control metrics such as the RNA Quality Number (RQN) and user defined Genomic Quality Number (GQN) aids in the determination of sample quality/integrity. This poster shows the unique use of the Femto Pulse System in high molecular weight gDNA separation and low input library preparation with subsequent analysis features highlighted.

### **P158. Sample QC with the Cell-free DNA ScreenTape Assay**

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*Background:* Quality control of nucleic acid starting material is essential to ensure the success of downstream experiments. Especially, Next Generation Sequencing (NGS) developed to a powerful tool in almost all genetic research and diagnostic areas. Due to the establishment of low input library protocols for NGS workflows sequencing of cell-free DNA (cfDNA) became possible. Since the downstream applications are often time-consuming and expensive, tight QC steps are required to ensure that samples are 'fit for purpose'. These QC steps can be performed with automated electrophoresis systems. *Methods:* Different cell-free DNA samples were evaluated for Sample quality with an Agilent 4200 TapeStation system and the Agilent Cell-free DNA ScreenTape assay. *Results:* Depending on preanalytical sample treatment or extraction methods the quality of cfDNA can vary. The results include a score to qualify cfDNA samples according to their contamination level with high molecular weight material. This allows defining a threshold for objective sample qualification prior to library preparation. Moreover, accurate quantification of cfDNA samples is essential to determine suitable input amounts for cfDNA library preparation prior to sequencing. *Conclusion:* Quality control of cfDNA is essential to ensure the success of downstream experiments. Automated electrophoresis systems standardize sample quality control and enable objective sample integrity assessment as well as the establishment of quality thresholds.

### **P159. Quality Control of DNA and RNA Samples Using the 4150 TapeStation System**

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Quality control (QC) of RNA and DNA samples is key for the success of any downstream experiment. Especially, Next Generation Sequencing (NGS) developed to a powerful tool in almost all genetic research and diagnostic areas. Since the downstream applications are often time-consuming, expensive and generate a lot of data, tight QC steps are required to avoid a 'garbage in-garbage out' situation.

The ideal QC solution is easy-to-use, economical and provides fast and unambiguous results also for very low concentrated samples.

Nucleic acid quality assessment can be standardized using automated electrophoresis systems to ensure that samples are 'fit for purpose'. Quality scores enable impartial sample comparison and allow defining a quality threshold for specific types of samples or preparation. For the objective quality evaluation of gDNA and RNA, the quality scores DNA integrity number (DIN) for gDNA and the RNA integrity number equivalent (RINe) for RNA can be assessed providing numerical values from 1 (degraded) to 10 (intact) for classification of samples. This poster exhibits the latest developments in nucleic acid sample QC and gives application examples – from gDNA and RNA to NGS libraries - evaluated with an Agilent 4150 TapeStation system.

### P160. Improved Clinical Utility of Next Generation Sequencing Panel Testing in Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

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**Background:** Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, inherited, potentially fatal channelopathy. Genetic testing is increasingly being used to confirm a diagnosis, often in a heterogeneous patient population. **Methods:** This is a retrospective review of patients ( $N = 134$ ) with a clinical suspicion of CPVT referred for genetic testing at Blueprint Genetics over a 5-year period (2013–2018). A subanalysis of diagnostic RYR2 variants (location, segregation) was performed. **Results:** A pathogenic (P) or likely pathogenic (LP) variant was identified in 27 patients (20.1%). Twenty patients (14.9%) had a diagnostic finding in a CPVT-associated gene: 62.9% in RYR2, 7.4 % in CALM1, and 3.7% in CASQ2 (biallelic). Four patients (14.8%) had a P or LP variant in KCNQ1, KCNJ2 or SCN5A, and three (11.1%) had a P or LP variant in a cardiomyopathy-associated gene (DSG2, DSP or PLN). All P/LP RYR2 variants were missense, except a deletion encompassing exon 3. Parental testing was performed in 11/17 cases where P/LP RYR2 variants were found; 8 (72.7%) variants were de novo. Enrichment of P/LP RYR2 variants in the four described hotspots ( $OR\ 50$ , 95% CI [29, 85],  $p < .0001$ ) was observed. **Conclusion:** 37% of patients with a diagnostic test result had a clinically significant variant in a gene other than RYR2. Of these, 26% had a genetic diagnosis of a cardiomyopathy or a channelopathy other than CPVT. This study supports the utilization of broad NGS panels for patients with a clinical suspicion of CPVT.

### P161. Improved Diagnostic Yield Through Optimized Mapping Quality and Coverage of the PKD1 Gene in ADPKD

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease caused primarily by mutations in PKD1 and PKD2. Analysis of PKD1 is challenging due to its large size, high GC-content and duplication

of the first 33 exons with a high degree of homology (90 - 99% identity) to six nearby pseudogenes (PKDIP1–P6). **Methods:** We evaluated the diagnostic yield and performance of two enhanced next-generation sequencing (NGS) panels covering 42 genes, for patients referred with cystic kidney disease ( $n = 131$ ). NGS was performed using the IDT xGEN Exome Research Panel with added custom probes and the Illumina NovaSeq 6000 platform. **Results:** A mean coverage of 192x was achieved. Mean coverage of PKD1 was 199x with 99.5% coverage at >20x. 52% of cases received a genetic diagnosis, with 63% and 13% of disease-causing variants identified in PKD1 and PKD2, respectively. Among PKD1 variants, P/LP variants were detected in 70% ( $n = 32$ ) of cases, including premature stop codons (35%), missense (28%), in-frame deletions (13%), frameshift indels (9%), splice site variants (6%) and gross deletions (9%). Variants of uncertain significance (VUS) were detected in 14 (30%) patients. 84% ( $n = 36$ ) of the variants were located in the duplicated region of PKD1. A number of PKD1 sequence variants (26%) were detected in exon 15 indicating a possible mutational hotspot. All observed P/LP PKD2 variants were truncating. **Conclusion:** An enhanced NGS platform provides clinical diagnostics with comprehensive coverage in difficult-to-sequence regions of PKD1.

### P162. Sequencing of RPGR-ORF15 Leads to Increased Diagnostic Yield in Patients with Inherited Retinal Dystrophies

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**Background:** Mutations in the RPGR gene account for 80% of cases of X-linked retinitis pigmentosa (XLRP). The C-terminal 567-aa exon ORF15 is a mutational hotspot for RPGR-associated RP, however, it generally performs poorly in standard sequencing-based assays due to a highly repetitive purine-rich sequence. We aimed to develop a comprehensive high-throughput clinical test for inherited retinal dystrophies, and to evaluate the performance of RPGR-ORF15 sequencing in a clinical patient cohort. **Methods:** 266 retinal dystrophy-associated genes were sequenced using an optimized whole exome workflow using Illumina NovaSeq 6000, including the difficult-to-sequence region in RPGR-ORF15. The prevalence and characteristics of RPGR variants was evaluated in a cohort of 1587 unselected patients with inherited retinal dystrophy. Custom Sanger sequencing methods were developed to confirm pathogenic and likely pathogenic RPGR variants. **Results:** Overall diagnostic yield was 58%. A molecular diagnosis in RPGR was identified in 5.7% (90/1587) of patients. Pathogenic/likely pathogenic variants consisted of 63 frameshifts (70.0%), 21 nonsense (23.3%), three missense (3.3%), two consensus splice site (2.2%), and one gross deletion (1.1%). Seventy-one out of 90 (79%) pathogenic/likely pathogenic variants were detected in ORF15, of which 28 (39%) were in the most difficult-to-sequence central region between amino acids p.824 and p.1077. **Conclusion:** Our data emphasizes the clinical importance of the difficult-to-sequence region in RPGR-ORF15 in XLRP patients, as it accounts for approximately 9% of XLRP cases. We have developed a high-quality diagnostic test for inherited retinal dystrophies. The high-quality NGS-based assay enables rapid and reliable molecular diagnostics of RPGR-ORF15 for inherited retinal dystrophies.