

Abstracts for the 41st Human Genetics Society of Australasia Annual Scientific Meeting

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Poster Presentations

CANCER GENETICS

1. NEW CHALLENGES IN TREATMENT FOCUSED GENETIC TESTING: A GENETIC COUNSELING PERSPECTIVE

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Germline mutations in cancer predisposition genes are increasingly being used to inform breast cancer treatment, resulting in an increased number of Familial Cancer Centre referrals for treatment-focused genetic testing (TFGT). TFGT requires urgency not typical in genetic testing for familial cancers. This urgency presents psychosocial challenges for our clients and, as genetic counselors, the necessity to increase our understanding of chemotherapy options and surgical interventions. A collaboration between genetic counselors and oncologists at the Parkville Familial Cancer Centre (PFCC) led to the development of an annotated clinical pathway, outlining typical breast cancer treatment options and the key time points where genetic testing may have an impact on treatment. Through the use of case studies, we highlight genetic counseling challenges faced as a result of TFGT, as well as psychosocial and clinical impacts specific to TFGT. The development of an annotated clinical pathway has informed our intake process for TFGT referrals. We are now better able to understand the possible psychosocial impacts of genetic testing for our patients undergoing TFGT and have an improved understanding of the common medical treatment pathways for breast cancer. Furthermore, the psychosocial challenges that arise during TFGT are important considerations as mainstreaming programs move this type of testing away from the genetics clinic and into an oncological setting.

2. WITHDRAWN

3. PARENT OF ORIGIN DEFINES RB1:c.2325+2T>C AS A VARIANT OF REDUCED PENETRANCE

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RB1 DNA sequence variants that encode premature termination of protein synthesis are a paradigm for assigning clinical classification. Conversely, the significance of variants predicted to effect aberrant splicing are too often open to confounding exceptions that complicate interpretation and diagnostic reporting. Here we describe the identification of RB1:c.2325+2T>C in a child with early onset disease, inherited from a father who is clinically normal, and ultimately traced back to the paternal grandmother with adrenocortical cancer. Intuitively, intronic changes at the canonical +2 position are predicted to affect aberrant splicing; however, the pedigree, albeit limited, does not conform to a textbook autosomal dominant mode of inheritance. Among less plausible reasons, this might suggest RB1:c.2325+2T>C is of reduced penetrance, or not causative. RNA studies by our laboratory confirmed splicing predictions, identifying in-frame loss of an entire exon in the predominant RB1 transcript. More importantly, however, our results demonstrate a significant difference in relative transcript ratios between father and son, with the aberrant transcript more highly expressed in the father. Evidence from the work of others provides an explanation for this unexpected expression pattern, from which it may be inferred that the RB1:c.2325+2T>C associated phenotype is dependent on the parent of origin. Not only do our findings have implications for genetic counseling of this family, but support a proposed mechanism by which RB1 variant alleles hitherto presumed of reduced penetrance may now be justifiably classified as such.

4. AUDIT OF REFERRALS FOR HIGH-GRADE SEROUS OVARIAN CARCINOMA TO GENETIC HEALTH SERVICE NZ NORTHERN

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Objective: Auckland City Hospital Oncology department and Genetic Health Service NZ — Northern hub are working toward piloting a mainstreaming model of genetic testing following the implementation of guidelines in 2013 to offer genetic testing to women diagnosed with high-grade serous carcinoma (HGSC) of the ovary, tube, or peritoneal aged 70 years and under, and the emerging treatment implications of BRCA genetic test results. The purpose of this audit was to determine the proportion of eligible patients with HGSC of ovary, tube, or peritoneal origin identified at gynaecologic oncology multidisciplinary meetings (MDM) referred for genetic counseling pre and post implementation of those guidelines; to ascertain the rate for non-attendance at genetics clinics and the rate of positive germline BRCA mutations. **Methods:** Eligible cases were identified from gynaecologic oncology MDM between January 1, 2012 to December 31, 2014. Genetic referrals were checked against the records of genetic services database to ascertain that referrals were received. Outcomes including attendance, genetic testing, and results were identified. **Results:** One-hundred-twenty-six patients were identified. Referral rates increased over the 3-year period from 40% in 2012 to 49% in 2014. Of the 61 patients referred, 56 attended genetic counseling, and 50 patients underwent BRCA mutation testing. A total of 24% tested positive for a germline BRCA mutation. **Conclusion:** Referral rates increased since the implementation of the national guidelines. BRCA mutation positive rate is compatible with current international data. The outcomes inform the move toward mainstreaming of BRCA germline genetic testing within the oncology setting.

5. MULTIPLE PILOMATRIXOMAS IN THREE UNRELATED CHILDREN AND LITERATURE REVIEW

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Background: Multiple pilomatrixomas in children may be sporadic or part of a genetic condition. We report three consecutive children with multiple pilomatrixomas referred to our service in a 14-month period and review the literature. **Case reports:** Child 1, a 4-year-old girl, had skin lesions on her arms, legs, back, and face since birth. Histology on a shoulder lesion showed pilomatrixoma. There was a maternal family history of skin 'cysts'. Child 2, a 13-year-old girl, had two biopsy-proven pilomatrixomas on her neck and face, enlarging over a 2-year period. Her mother's maternal half-sister had a history of skin 'cysts'. Child 3, a 15-year-old girl, had fast-growing lesions removed from her scalp at age 9 months and chest at 9 years. Seven more lesions were removed from her eyebrow, neck, and chest. These were proven pilomatrixomas. Her brother had three pilomatrixomas removed from his neck, back, and arm at age 13, 15, and 16 years. There was a maternal family history of skin 'cysts'. All children had normal development and no history of muscle weakness or learning difficulties. There was no family history of bowel cancer or polyps for all three children. Genetic testing was undertaken. **Results:** The results of the genetic testing will be presented. **Discussion:** Pilomatrixomas are rare, benign skin tumors derived from follicular cells. They have been reported in various genetic conditions. We will discuss the results of the genetic testing and a review of the literature.

6. IDENTIFICATION OF GENETIC VARIANTS ASSOCIATED WITH RISK OF ENDOMETRIAL CANCER

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Endometrial cancer, a neoplasm of uterine epithelial lining, is the most commonly diagnosed gynecologic malignancy in developed countries. Approximately 3–5% of endometrial cancer is caused by inherited pathogenic variants in one of the mismatch repair genes (MMR), MLH1, MSH2, PMS2, or MSH6. Tumor MMR deficiency can be used as a molecular marker to identify such cases at diagnosis, and direct management of carrier relatives who are at high risk of MMR gene-related cancers. The aim of this project is to identify novel genes and genetic variants that underlie familial endometrial cancer. A total of 35 Australian National Endometrial Cancer Study (ANECS) cases were selected for Next Generation Sequencing (NGS) on the basis of MMR proficient tumor phenotype as determined by immunohistochemistry; the proband had at least one affected relative with a DNA sample available for analysis and also a cancer diagnosis (excluding skin cancer due to the significant role of environmental factors in the Australian setting, and endometrial cancer after breast cancer diagnosis due to possibly confounding by tamoxifen exposure). A list of genes previously implicated in cancer, increased BMI (a strong risk factor for endometrial cancer), as well as variants located in or near known endometrial cancer risk loci identified by genome wide association study have been used to prioritize candidate genes within the NGS data. Preliminary analysis focusing on truncating variants has identified a known cancer risk gene not previously implicated in endometrial cancer in a proband and one cancer-affected relative. Analysis of other variants is ongoing.

7. BAP1 MUTATIONS PREVALENCE AND ASSOCIATED TUMOR SPECTRUM IN A COHORT OF AUSTRALIAN UVEAL MELANOMA CASES

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The discovery of germline mutations in the BRCA1-associated protein 1 (BAP1) gene causing the BAP1 tumor predisposition syndrome (BAP1-TPDS) has elucidated a possible explanation behind previously unexplained high density of cancer in certain families. BAP1-TPDS has been linked primarily to uveal melanoma (UM) and mesothelioma but also cutaneous melanoma, renal cell carcinoma, cholangiocarcinoma, basal cell carcinoma, and meningioma. The BAP1-TPDS is a relatively new field of research, hence the number of families reported worldwide to date is low ($n = 94$). UM is the most common malignancy reported in these families and is associated with early onset (age 16 years) and more aggressive disease in comparison to BAP1 wild type UM individuals. We aim to determine the prevalence and penetrance of BAP1 germline mutations within a cohort of UM cases recruited through the Queensland Ocular Oncology Service (QOOS) and establish the associated spectrum of other tumors within their families. Patients seen at the QOOS will be approached for recruitment into the study cohort; DNA will be collected via blood or saliva along with tumor samples if applicable. Family history of cancers will be obtained and consent and samples from family members will also be sought for mutation analysis. We will endeavor to confirm all self-reported cancers, commonly through the Queensland Cancer Registry. BAP1 mutation status

will be determined by Sanger sequencing. We hope to significantly add to this under researched group of families in order to better evaluate the penetrance and tumor spectrum associated with these mutations.

8. TOWARD PERSONALIZED CANCER TREATMENT: 'CANCER 2015' — A PROSPECTIVE, POPULATION-BASED CANCER GENOME COHORT STUDY

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Cancer 2015 is a large-scale prospective population-based cancer genomic cohort study. The study aims to test a new model of cancer diagnosis and treatment, with a specific focus on integrating molecular pathology into routine clinical practice. Newly diagnosed adult patients with solid cancers were recruited across five hospitals in Victoria, Australia, between 2012 and 2016. The cohort consists of 3,000 treatment-naïve cases of 22 solid tumor types with associated data, including clinico-pathological data, cancer genomic profiles, health outcomes, health resource use, and health-related quality-of-life data. The cohort is generally proportionate to the Victoria Cancer Registry (VCR). Patients aged over 50 years account for approximately 76% of the cohort. Genetic mutations were determined on targeted gene panels of common cancer genes with a success rate of 78%. Depending on testing panels, variants have been identified in 39–68% of cases that passed QC metric filters. Colorectal cancer has the highest frequency of mutations with 93% cases carrying at least one mutation and an average 3.66 mutations per patient. Clinically actionable variants were identified in approximately 31% cases. Potentially druggable mutations were also found in cancers that are currently lacking therapeutic options for effective tumor control. Somatic variants identified in the cohort are curated in the PathOS database, in the context of the biological and clinical significance of the mutation, gene, and tumor, providing a valuable resource for future clinical and research applications. The Cancer 2015 biospecimen and data are available to the cancer research community. Further information is available at www.cancer2015.org.

9. A META-ANALYSIS OF SURVEILLANCE IN TP53 MUTATION CARRIERS USING WHOLE BODY MAGNETIC RESONANCE IMAGING

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Background: Germline TP53 mutation carriers have a very high lifetime risk of multi-organ cancer. Clinical risk management guidelines are very limited for these individuals. Surveillance using whole body magnetic resonance imaging (WB-MRI) may have utility in this high-risk population. **Aim:** To assess the clinical utility of WB-MRI in TP53 mutation carriers as part of a baseline assessment. **Methods:** Surveillance studies in TP53 mutation carriers utilizing WB-MRI were identified through the Li Fraumeni Exploration Research Consortium. Data was extracted from each cohort and synthesized. Random effects meta-analysis methods were used to estimate proportions. **Results:** A total of 578 individuals (376 female) undergoing surveillance from 13 studies across 6 countries were included. Two hundred and twenty five lesions requiring further investigation were detected in 173 individuals. Overall, 31% (95%CI 26–35%) of individuals had one or more investigable lesions. Forty-two malignant lesions were diagnosed in 39 individuals. Thirty-five of these malignancies were localized primary cancers that went on to be treated with curative intent. Overall, 7% (95% CI 5–9%) of individuals were found to have one or more new primary cancers. Eighteen percent (95% CI 12–27%) of investigable lesions were determined to be new primary cancers. Malignancies included those recognized as part of the Li Fraumeni syndrome spectrum as well as cancers of the kidney, lung, thyroid, prostate, and bowel. **Conclusion:** The findings support the use of WB-MRI as part of a baseline surveillance assessment in TP53 mutation carriers.

10. INQUISIT — INTEGRATED EXPRESSION QUANTITATIVE TRAIT AND IN SILICO PREDICTION OF GWAS TARGETS

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Genome-wide association studies have been phenomenally successful, but the major bottleneck in understanding the mechanisms underlying these loci is the determination of the target genes affected by the candidate causal risk variants (CCRVs). We have identified 179 loci associated with breast cancer risk but identified target genes at only 14 of them. We therefore developed INQUISIT to rank predicted target genes to prioritize functional assays and underscore pathway analyses. We reasoned that most CCRVs act via distal gene regulation, proximal gene regulation, or by impacting the protein product, and applied different sets of weights for each of these scenarios. Points are awarded to each gene based on

chromatin interaction data, enhancer annotations, and expression quantitative trait loci (eQTL) analysis of all nearby genes, and integration of transcription factor (TF) ChIP-seq data for specific proteins in breast cells shown to be positive predictors of the CCRVs. The intersection of CCRVs, enhancers, and these TF binding sites resulted in up-weighting of the associated gene. Unexpressed genes and genes across topologically associated domain boundaries were down-weighted. Promoter variants were assessed for characteristic chromatin signatures, putative functional TF binding site overlap, gene expression data, and eQTLs. Intragenic variants were evaluated for consequences of coding and splicing changes. Among the 689 protein coding target genes predicted, we found a strong enrichment for established breast cancer driver genes ($p < 10^{-6}$), which increased with increasing INQUISIT score level ($p = 5.7 \times 10^{-12}$). These results provide further evidence for the link between the germline and somatic genome of breast cancer.

11. DISPARITIES IN HEALTH CARE AND THE COLOR CANCER GENE PANEL TEST

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Color (www.color.com) is a company founded near Silicon Valley in the USA in April 2015 with the goal of providing high-quality cancer gene tests to everyone, everywhere, preferably ordered by a physician. Color now offers a 30 cancer gene panel test, cascade testing to other family members, and a telephone genetic counseling service. Brisbane Genetics started using the Color brand test in June 2016. It was not the first cancer gene panel test used by this clinic. As of March 2017, about 212 tests have been completed, and 13% had a pathogenic or likely pathogenic result. VUS are not reported by choice. Cancer gene panel tests have entered clinical practice. Many providers started offering these tests after the US Supreme Court decision in 2013 regarding the Myriad Genetics BRCA1/2 gene patents. The Color company actively tries to overcome the problem of access (or disparity) to cancer gene tests in the USA and elsewhere. For example, Color has partnered with the Pink Hope organization in Australia to provide a subsidized test. The Color test is using next generation sequencing as part of a service that is very different to traditional pathology providers. This presentation will discuss the use of the Color test at Brisbane Genetics, and how this test has changed service delivery in this one small practice.

12. POINT MUTATION IN P14ARF-SPECIFIC EXON 1B OF CDKN2A CAUSING FAMILIAL MELANOMA AND ASTROCYTOMA

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Melanoma can, rarely, be inherited as a dominant monogenic disorder. Eight genes have been previously identified; and mutations in CDKN2A account for over 85% of all mutation-positive families. CDKN2A encodes two transcripts, p16 and p14ARF, both of which have been implicated in melanoma, though variants in p16 account for 95% of CDKN2A-positive families. CDKN2A has also been implicated in cancer syndromes. We identified a 17-year-old proband with melanoma and astrocytoma, with a family history of

dominant melanoma with variable penetrance. Sanger sequencing excluded mutations in the CDKN2A p16 transcript. Whole-exome sequencing identified a novel missense mutation (c.193G>A: p.Gly65Ser) in the final base of the p14ARF-specific exon 1β of CDKN2A, a position critical in splice site recognition. This mutation was present in the proband and her unaffected grandfather, an obligate carrier. Sequencing of p14ARF cDNA did not reveal an aberrant transcript, suggesting lack of transcription or transcript instability. An uncommon variant in ATM (c.146C>G:p.Ser49Cys), previously associated with increased melanoma risk, was also identified in the proband but not her (unaffected) grandfather. Penetrance of the CDKN2A splice site mutation may have been modified by this variant allele of ATM. Deletions of exon 1β of CDKN2A have previously been identified in melanoma astrocytoma syndrome; this is the first case of melanoma astrocytoma syndrome secondary to a splice site mutation affecting the CDKN2A p14ARF transcript.

13. UPTAKE OF POLYGENIC RISK INFORMATION AMONG WOMEN AT POTENTIALLY HIGH BREAST CANCER RISK

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Background: Despite increasing evidence for the utility of polygenic risk in families at high risk of breast cancer, research findings are yet to be integrated into clinical practice. This reflects the status of polygenic risk as an emerging technology and the limited evidence base on the psychosocial and behavioral outcomes of offering such testing. **Aims:** To ascertain the important psychosocial and behavioral implications of testing for polygenic breast cancer risk in the existing cohort the Variants in Practice (ViP) study. **Methods:** Four hundred women enrolled in ViP, who have either a high or low polygenic risk score (PRS), and whose personal and/or family history breast cancer remained unexplained after genetic testing for known cancer predisposition genes are being invited to participate in this study. Participants complete a baseline questionnaire assessing their knowledge of hereditary breast cancer, current breast cancer screening behaviors, psychological wellbeing, and intention to receive personal PRS results. **Results:** As of April 2017, 69/74 (93%) participants reported interest in receiving their PRS result, with 20/74 (27%) having received their results. The mean knowledge score among participants was 6 (max score = 12), and 20% and 8% of participants scored over the cut-offs for cancer-specific distress and general depression, respectively. **Conclusion:** While there is strong interest in receiving personal PRS result among women at high risk of breast cancer, the psychosocial and behavioral implications should be carefully considered. Data collection is ongoing, with additional data regarding uptake of results and short-term impact of receiving results to be presented.

CLINICAL GENETICS**14. GENETIC VARIANTS IN HUMAN IMMUNODEFICIENCY**

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Background: Whole exome sequencing (WES) trio analysis of an undiagnosed immunodeficiency case with severe lymphopaenia and neutropaenia (Proband) and parents was performed previously. A novel X-linked single base mutation in the MSN gene and two rare damaging amino acid-changing SNPs in the TET2 and NLRP8 genes were identified and validated by Sanger sequencing and found not to be present in the parents and sibling, who appear to be healthy. A large putative ~4 kbp deletion in the SIRPB1 gene was also identified and has been further investigated more recently. **Aim:** To determine potential causal links between the impact of the mutations and involvement in the Proband's disorder. **Methods:** Primary PBMC cultures of the Proband, parents, and healthy control will be used for further investigation of the mutation, polymorphisms, and putative deletion previously identified by WES. This study will perform *in vitro* gene expression and protein studies and will use CRISPR/Cas9 technology in commercial lymphoid cell lines as functional analytic methodologies. **Results:** The putative deletion in SIRPB1 was further investigated by PCR and Sanger sequencing and found not to be a ~4 kbp homozygous deletion, but rather a possible rearrangement not present in the parents. Preliminary Q-PCR analysis showed a significant difference between the Proband and a universal human reference RNA template for TET2 ($p = .029$) and SIRPB1 ($p = .006$) gene expression by two-tailed *T*-tests. **Discussion:** It is anticipated that these investigative studies will form the basis of CRISPR/Cas9 rescue phenotype experiments in the Proband and will improve personalized treatment strategies for other lymphoid abnormalities.

15. A TARGETED ANALYSIS APPROACH TO WHOLE EXOME SEQUENCING FOR EPILEPSY DIAGNOSISPaul Dunn^{1,2,3}, Neven Maksemous^{1,2,3}, Cassie Albury^{1,2,3}, Robert Smith^{1,2,3}, Heidi Sutherland^{1,2,3}, Larisa Haupt^{1,2,3}, and Lyn Griffiths^{1,2,3}¹Genomics Research Centre, Brisbane, QLD, Australia²Institute of Health and Biomedical Innovation, Brisbane, QLD, Australia³School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

Background: Epilepsy classifies a number of seizure disorders caused by excessive and abnormal brain cell activity. A total of 70–80% of all epileptic cases are thought to be caused by one or more genetic mutations, catering to a highly variable phenotypic expression. Recent advancements in next generation sequencing (NGS) have contributed to an increased understanding of the genetic contribution to epilepsy disorders. Despite this, as yet, no accurate and cost-effective diagnostic test exists. The development of such a test would have significant prognostic implications for patients and their families. **Aim:** This study aims to apply a whole exome sequencing (WES) approach to epilepsy diagnosis using targeted analysis of ~395 genes identified to be associated with epilepsy. **Methods:** WES was completed on 20 samples using the Ion AmpliSeq™ Exome RDY Kit. All data were analyzed using an in-house bioinformatic pipeline, analyzed following filtering and prioritization of variants based on gene ontology, associated pathways, minor allele frequencies, and a number of *in silico* predictive functional scores. Initial work focused on four samples with a known SCN1A gene mutation previously identified using our NGS diagnostic neurogenetic panel. An additional 16 samples with no mutation in the SCN1A gene were then examined by WES and targeted analysis in an effort to identify mutations in other potential genes contributing to their epilepsy phenotype. **Conclusions:** It

is hoped that this research will develop an improved diagnostic test for epilepsy patients and provide more refined treatment options.

16. A CHILD WITH COMPOUND HETEROZYGOUS DESMOPLAKIN MUTATIONS: A NEW PHENOTYPE?Julie McGaughan^{1,2}, Joanna Crawford³, and Cas Simons³¹Genetic Health Queensland, Brisbane, QLD, Australia²University of Queensland School of Medicine, Brisbane, QLD, Australia³Institute for Molecular Biosciences University of Queensland, Brisbane, QLD, Australia

The proband was first referred at 14 months of age. He had developed an extensive ichthyotic rash and failure to thrive, requiring tube feeding. He developed thickened abnormal fingernails and had very sparse hair. His dentition was late but appeared normal. A diagnosis of Hutchison–Gifford progeria had been considered and excluded on genetic testing. On review, he had been diagnosed with alopecia and palmar and plantar keratoderma. He also had significant dry skin and eczema. He had normal sweating. He had a number of allergies. His development was normal. As no clear unifying diagnosis was made, he was included in a WES study. This showed compound heterozygosity for a disruptive in-frame deletion and a premature stop codon in the desmoplakin (DSP) gene. It was confirmed the mutations were in trans. Previous case reports of biallelic variants in this gene have been made. They have included dilated cardiomyopathy and woolly hair with keratoderma, skin fragility-woolly hair syndrome, and lethal acantholytic epidermolysis bullosa. On the basis of this result, a cardiac evaluation was carried out and demonstrated early cardiomyopathy. This patient has dermatological features different from those reported and we believe this represents a new phenotype associated with biallelic mutations in DSP.

17. CLINICAL AND MOLECULAR CHARACTERISATION OF PATIENTS WITH BECKWITH WEIDMAN SYNDROME AND OTHER OVERGROWTH SYNDROMES

Gargi Pathak and Sharron Townshend

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Clinical and molecular characterization of patients with Beckwith–Weidman syndrome (BWS) and other overgrowth syndromes to predict appropriate surveillance measures. **Background:** The objective of this study is to audit the clinical and molecular features in BWS and other overgrowth syndromes presenting to GSWA. **Aim:** To identify the relation between genotype and phenotype with the aim of improving tumor surveillance. (1) Evaluate the merit of looking for mosaicism in context of different overgrowth syndromes and consider enhancing existing overgrowth gene panels. **Method:** A retrospective audit will be conducted in GSWA, collecting data on clinically diagnosed and molecularly confirmed BWS and other overgrowth syndromes, using the online patient records software and hospital charts. The study data will be analyzed for genotype–phenotype correlation for BWS in our population. The tumor risk will be studied with different genotypes to facilitate appropriate surveillance. Considering the increasing number of other overgrowth syndromes being diagnosed, and improvement in genetic technology, the merit of looking for mosaicism and other overgrowth gene panels will also be investigated. The results will then be compared to other published literature worldwide toward meaningful outcomes. **Significance:** This audit will improve the current tumor surveillance guidelines for overgrowth syndromes and may improve the molecular characterization for some patients.

18. COMMON VARIANTS ASSOCIATED WITH MACULAR TELANGIECTASIA TYPE 2 (MACTEL)

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Background: MacTel is a rare late-onset neurovascular disease of the eye that leads to loss of central vision. Clinical symptoms include angiogenesis, abnormal blood vessel growth, crystal deposits, and pigment plaques, all in the area of the macula. There is currently no known effective cure or treatment for the disease. It is a complex disease with known environmental risk factors such as BMI, diabetes, and smoking, and suspected genetic risk factors. **Aim:** To identify genes involved in MacTel. **Methods:** We performed a whole genome-wide association study (GWAS) with 476 cases and 1,733 controls. **Results:** We identified and replicated five loci of major interest. **Discussion:** The strongest associated loci were found on chromosome 5. This specific locus has previously been associated to variation in retinal blood vessel calibres. The MacTel risk alleles were the same as associated with increased vessel size. The other four loci (on chromosomes 1, 2, 3, and 7) have previously been associated to the glycine/serine metabolic pathway. The MacTel risk alleles were the same as associated with decreased blood serum levels of glycine and serine. As a follow-up study, we analyzed the glycine and serine blood serum levels in 50 MacTel cases and 50 controls, and found a significant reduction in the MacTel cases. We therefore identified a new pathway that is likely to be involved in the etiology of MacTel, thereby opening the door for potential new treatments and cures.

19. RAPID TESTING TECHNIQUE FOR PREIMPLANTATION GENETIC SCREENING ON THE BGISEQ PLATFORM

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In the present, some doctors prefer fresh embryo transfer in IVF cycles, because good viability embryos can improve pregnancy rate. PGS that could be completed within 24 hours is very popular. We developed a rapid 15–24 hours PGS technique with different library construction methods (Tn5 and one tube reaction) on BGISEQ (BGISEQ-50 and BGISEQ-500). Single cell and multiple cells of 67 different cell lines purchased from Coriell were picked up using micromanipulation, and were amplified by PicoPLEX[®] WGA Kit. We used Tn5 and one tube reaction to construct WGA products libraries, sequenced on BGISEQ-50 and BGISEQ-500, respectively. Meanwhile, we used Tn5 to construct libraries of three single cell samples and seven multiple cells samples without WGA and sequenced on BGISEQ-500. BGISEQ is powered by combinatorial Probe-Anchor Synthesis (cPAS) and DNA Nanoballs (DNB) technology, has fewer replication mistakes. Windows selection, GC correction, and copy number analysis were performed on sequencing reads. Analysis results would be compared with the known karyotypes. The 43 >4M CNVs cell lines, 15 aneuploid cell lines, and 9 negative cell lines from 67 cell lines could be all detected successfully on BGISEQ-50 and BGISEQ-500, respectively. Two out of three single cell samples and seven multiple cells samples without WGA were also successfully detected. For now, the Tn5 library construction of cells without WGA needs further optimization, in consideration of their high duplication rate. In the future, we would convert this rapid PGS method into clinical application for fresh embryo transfer after more experimental verification.

20. THE MULTIDISCIPLINARY PEDIATRIC RENAL GENETICS CLINIC: A MODEL FOR MAINSTREAMING GENETICS IN MEDICINE

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Our understanding of the genetic factors involved in many conditions is continually evolving, and the availability of genomic testing is rapidly expanding, creating a necessity for new services, new ways of working, and modified professional roles in order to maximize the benefit to patients and families. The multidisciplinary clinic is one model to achieve this and integrate genetics into mainstream medicine. The joint Royal Children's Hospital and Victorian Clinical Genetics Services Renal Genetics Clinic was established in February 2016 with the aim of improving diagnosis rates and informing management in patients with suspected genetic renal disease. The clinic team includes a nephrologist, clinical geneticist, genetic counselor, and administrative support, with each member of the team contributing unique expertise and benefitting from opportunities to cross-train and upskill. In order to evaluate processes and outcomes, as well as inform future practice, a retrospective clinical audit of the first 14 months of clinic operation was conducted. Patients typically attended for one or more of clinical diagnostic assessment, genetic counseling, genetic/genomic testing, and/or research recruitment; and benefitting from multidisciplinary case review before, during, and after appointments. Data for 34 patients is presented, including instances of genetic diagnosis leading to altered management. Results of the audit provide insight into the first pediatric multidisciplinary renal genetics clinic in Australasia. Outcome data has demonstrated benefits for patient care, as well as opportunities for biological relatives to access genetics services. Anecdotal evidence supports staff satisfaction with the service model and professional development opportunities.

21. EXPERIENCES AND ATTITUDES OF ADULTS WITH NEUROFIBROMATOSIS TYPE 1 ATTENDING A SPECIALIST SKIN CLINIC

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Background: Skin manifestations of neurofibromatosis type 1 (NF1), which includes multiple cutaneous neurofibromas and pigmented macules, can affect adults clinically and psychologically. The appearance of these lesions can result in emotional distress and social isolation. In 2015, a novel clinical genetics dermatological service dedicated to the clinical management of the skin manifestations of NF1 was initiated at Royal North Shore Hospital in Sydney. The usefulness and limitations of this service from a patient's perspective have yet to be evaluated. **Aim:** To explore patients' views and experience of attending the skin clinic. **Methods:** Fifteen patients affected by NF1 (age ≥ 18 years), who attended the skin clinic have been invited to participate in semi-structured interviews. To date, 7/11 consented participants have been interviewed and recruitment is ongoing. Data is being coded with concordance by three coders and analyzed using inductive thematic methodology. **Results:** Four emerging themes have been identified: (1) reported skin concerns: skin manifestations, their psychological and functional impacts; (2) high perceived value: reported current and potential future benefits of the skin clinic for self and others; (3) treatment:

satisfaction, preferences; and (4) recommendations for service provision: management of expectations, suggestions for improvement. **Conclusions:** Current data suggests that adults place strong value on dedicated clinical services to address the skin symptoms of NF1, even where cosmetic improvement is not significant. Findings of this study may increase awareness of the cosmetic burden associated with NF1 and illustrate the benefits of a dedicated clinical service to manage skin concerns.

22. THE EXPERIENCE OF INITIATING A MULTI-DISCIPLINARY TUBEROUS SCLEROSIS COMPLEX CLINIC IN NSW

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Background: Tuberous sclerosis complex (TSC) is a multi-system, autosomal dominant condition associated with benign tumors in multiple organs, epilepsy, intellectual disability, and autism. Presymptomatic/early diagnosis, surveillance, and management may improve neurodevelopmental and tumor outcomes. It is therefore an ideal model condition to assess the benefits of introducing a multidisciplinary clinic with the aim of improving clinical outcomes. The TSC multidisciplinary management clinic at Sydney Children's Hospital (SCH) was established in 2006. It has become the primary referral center for pediatric patients with TSC in New South Wales. **Aim/Methods:** Retrospective ascertainment of all TSC patients in the statewide genetics database. Subsequent review of new paediatric TSC patients seen at SCH between 2001 and 2015. We assessed whether the clinic has made a difference in the diagnosis, management, and monitoring of TSC patients. **Results:** One hundred twenty nine patients had a diagnosis of TSC in Trakgene. The number of patients seen by a genetics service increased following the establishment of the clinic ($p < .01$). (1) Of the 100 patients seen at SCH, the number of antenatal and early diagnoses before onset of seizures has increased over the years ($p < .05$). (2) 41/44 (93%) of those seen within the last 12 months were compliant with surveillance guidelines. (3) Since 2010, 19 patients were commenced on oral mTOR inhibitors mostly for neurological indications. **Conclusion:** TSC provides a good example of the benefits a multi-disciplinary clinic for the management of a multi-system condition. The clinic assists engaging with target cohorts for new and future management, such as mTOR inhibitors.

23. THE AUSTRALIAN ATHOME™ INFUSION SERVICE: EXPERIENCE OVER 6 YEARS

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The Shire-funded ATHOME™ infusion service provides home infusion support for eligible Australians prescribed intravenous agalsidase alfa ghu* (AAG) or velaglucerase alfa ghu* (VAG) for Fabry and Gaucher Disease, respectively. ATHOME aims to reduce the burden on patients and healthcare infrastructure while promoting improved care and education. Treating physicians may enroll patients after a minimum 12 AAG or 3 VAG in-hospital infusions. AAG or VAG is delivered to the home or workplace and an IV administration-trained registered nurse prepares and administers the infusion and monitors safety during the procedure. The ATHOME service commenced in Australia in July 2010 for AAG patients and May 2013 for VAG patients. As of August 31, 2016, 40 AAG and

22 VAG patients have been enrolled with an average time in the program of 48 and 44 months, respectively and high patient retention (80.0% for AAG patients and 86.4% for VAG patients). Most planned infusions were administered (97.5% and 98.1% in AAG and VAG patients, respectively), with 98.1% and 94.3% of these delivered within 2 days of the originally scheduled date. Continuity of care with a single nurse over the entire period of enrolment has been achieved in 64.1% of AAG patients and 76.2% of VAG patients who continue to participate. Through a network of specially trained registered nurses, the ATHOME infusion service successfully offers enrolled patients the convenience and flexibility to receive treatment in the home or workplace environment with high adherence rates and continuity of care. *ghu denotes 'gene activated human'.

24. A RARE CASE OF HORIZONTAL GAZE PALSY WITH PROGRESSIVE SCOLIOSIS

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Introduction: Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive condition, described in several dozen families worldwide. Mutations in ROBO3 were identified as the cause in 2004. The rarity and lack of familiarity with HGPPS can present a diagnostic challenge. **Case Report:** An 18-month-old girl presented to clinic to be assessed for a unifying diagnosis for her features. Her prenatal and antenatal progress was unremarkable. She was first noted by her parents to have nystagmus at 3 weeks of age. She had developmental delay (sitting at 11 months, walking at 2½ years). The ophthalmologist diagnosed her with Duane syndrome Type 3 at 1 year. She also had significant torticollis and plagiocephaly. She developed scoliosis from 1 year of age that was rapidly progressive and required bracing. Her family history had a maternal half-sister with scoliosis. There were no distinct diagnostic features on examination. She was hypotonic with a broad nasal bridge and deep set eyes, with scoliosis and a Duane anomaly. Her microarray was unremarkable. A review of the literature suggested HGPPS as a possible diagnosis. Targeted testing of the ROBO3 gene showed a compound heterozygous state for two novel mutations. Segregation testing showed the parents to be heterozygous carriers. **Discussion:** This case is a rare condition. Increased familiarity with HGPPS will lead to earlier recognition and diagnosis. A review of published cases will also be presented.

25. TORIELLO-CAREY SYNDROME AND COFFIN-SIRIS SYNDROME, IS THERE A GENETIC LINK BETWEEN THESE TWO SYNDROMES?

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Toriello-Carey syndrome (TCS) is characterized by facial dysmorphism, micrognathia, intellectual disability, absent corpus callosum, and other congenital anomalies. The aim of this presentation is to highlight the fact that there is a lack of distinctive diagnostic clinical features in patients with TCS. Our patient is part of a study performed on 10 patients with a clinical diagnosis of TCS. Exome sequencing was performed in these patients. Our patient has significant developmental delay, short stature, distinctive face, micrognathia, cleft palate, congenital heart disease, absent corpus callosum, and many other congenital anomalies, suggesting a clinical diagnosis of TCS. She has a mutation in a gene known to cause

Coffin–Siris syndrome. As per literature, no definite criteria exist for the diagnosis of TCS. This presentation highlights that TCS may not be a distinctive syndrome and is probably a part of a spectrum of disorders involving a common genetic pathway. More cases like this need to be reported, which may help in understanding clinical and molecular odyssey associated with TCS.

26. CONGENITAL MYOPATHY DUE TO 14Q22 DELETION: EXPANDING THE PHENOTYPE OF FRIAS SYNDROME

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Interstitial deletions of 14q22.1–q22.3 are associated with Frias syndrome, a contiguous gene deletion syndrome characterized by short stature, facial anomalies, syndactyly, and postaxial polydactyly. Features have been attributed to haploinsufficiency of BMP4, as heterozygous variants in BMP4 have been identified in individuals with syndromic microphthalmia and orofacial clefting. Myopia, polydactyly, and syndactyly have been reported in some individuals with heterozygous BMP4 variants. BMP4 encodes a member of the bone morphogenetic protein (BMP) family of secreted proteins, is important in early embryogenesis and has been implicated in fetal skeletal muscle development. We describe a two-generation family consisting of three individuals with a 1.9 Mb microdeletion of 14q22.1–q22.2. This deletion encompasses 10 genes, two of which are OMIM listed, BMP4, and DDHD1. In addition to features known to be associated with Frias syndrome, including post axial polydactyly, hypertelorism, and exophthalmos, the adult proband had minimally progressive childhood-onset muscle weakness and ptosis. His children have similar facial features to their father but do not appear to have significant muscle weakness at this stage. Myopathy has not previously been described in association with Frias syndrome although motor developmental delay and hypotonia have been described in affected children. This family illustrates the phenotypic heterogeneity of chromosome 14q22 microdeletion and suggests that myopathy may be associated with this condition, consistent with previous reports of the role of BMP4 in fetal skeletal muscle development.

27. BRACHYTELEPHALANGIC CHONDRODYSPLASIA PUNCTATA: THREE CASES HIGHLIGHTING THE CLINICAL UTILITY OF INVESTIGATIONS AND ASSOCIATED MEDICAL COMPLICATIONS

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Brachytelephalangic chondrodysplasia punctata (BCPD) (CDPX1, OMIM: #302950) is a rare skeletal dysplasia caused by arylsulfatase E (ARSE) deficiency. The clinical diagnosis is based on distinctive physical and radiographic features. Phenocopies secondary to maternal SLE, prenatal exposure to phenytoin, alcohol and warfarin, and maternal Vitamin K deficiency are reported in peer-reviewed journals. There are no reported manifesting females with molecularly confirmed pathogenic ARSE mutation. We highlight three cases, a female and two males, presenting with typical dysmorphism

and skeletal features consistent with BCPD. The mother of the affected female infant has a high autoantibody level (ANA 1280) and otherwise normal investigations. One male patient, now an adult, has had normal ARSE sequence analysis and confirmed maternal SLE. He has cervical spinal fusion (C5–C7) with spinal cord compression and had hip dysplasia which required surgeries. The other male infant presented acutely unwell with suspected seizures, respiratory distress, and hypotonia. Spine MRI confirmed marked cervical (C2/C3) spinal stenosis and he had abnormal polysomnography. We discuss the differential diagnosis of BCPD and the clinical utility of associated investigations. We highlight the rare but significant cervical complication that affects clinical prognosis.

28. GENDER DIFFERENCES IN CHILDREN WITH DOWN SYNDROME AND CONGENITAL HEART DISEASE

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Background: The life expectancy at birth of patients with Down syndrome (DS) between 1953 and 2000 was 58.6 years (Glasson EJ et al., 2002) as compared to 16.2 years between 1948 and 1957 (Collmann RD et al., 1963). Contrary to female longevity in the general population, males with DS had significantly greater life expectancies than females with DS in Western Australia (Glasson EJ et al., 2003). In Japan, the life expectancy at birth also increased to 48.9 years for 1,052 DS who were born between 1966 and 1975 (Masaki M et al., 1981). **Hypothesis and Aim:** We hypothesized that shorter life expectancy of female DS may be attributed to increased prevalence of congenital heart disease (CHD), especially of severe CHD from which prognosis is poor. Our study was designed to clarify gender differences of the prevalence and severity of CHD in Japanese DS. **Methods:** Our data are based on medical records from five hospitals in Tokyo and two questionnaires to patients' parents. **Results:** The total number of patients with DS was 1,310 (626 females, 684 males). The rate of complication of CHD in females (354; 57%) was significantly higher than that in males (338; 49%) ($p = .010$). Significantly more females underwent surgery for CHD (199; 32%) than males (175; 26%) ($p = .018$). The most common cardiac anomalies (main lesions) were VSD, ASD, AVSD, PDA, and TOF. **Conclusions:** The higher prevalence and graver severity of CHD in females may in part attribute to shorter life expectancy in female DS.

29. CATASTROPHIC OUTCOMES OF BASILAR ARTERY MEGADOLICHOECTASIA IN A FAMILY WITH FABRY DISEASE

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Background: Fabry disease (FD) (OMIM 301500) is an X-linked lysosomal storage disease caused by a mutation in the GLA gene resulting in deficiency of the lysosomal enzyme α -galactosidase A. It leads to the accumulation of globotriaosylceramide within vascular endothelium due to impaired glycosphingolipid metabolism. There is a wide spectrum of disease manifestations, including cardiomyopathy, nephropathy, and cerebrovascular disease. Within the central nervous system, a small vessel vasculopathy occurs, with patients predisposed to vascular anomalies and impaired vascular

function. Sequelae can include white matter lesions, vertebrobasilar artery ectasia, and posterior circulation cerebrovascular events. *Case Series:* Megadolichoectasia with thrombosis has previously been reported only in small case series of first-degree and distant family members. We present a large Australian FD family with five first-degree relatives having basilar artery megadolichoectasia with thrombosis and/or posterior circulation cerebrovascular ischaemic events. The family had the GLA missense mutation M284T, causing a classical FD phenotype. This mutation may be an additional risk factor for intracranial aneurysms. Cerebrovascular disease progression directly resulted in three deaths and strokes with significant morbidity in the other two. The most severely affected members also had severe cardiomyopathy and end-stage renal disease. While vascular intervention was considered in each patient, the location and size of these aneurysms combined with the high risk of injury associated with the procedure, precluded stenting with available intervention techniques. Unfortunately, enzyme replacement therapy did not appear to delay the progression of cerebrovascular complications in this family.

30. WITHDRAWN

31. WITHDRAWN

32. EXOME SEQUENCING ARTIFACTS: HOW TO IDENTIFY THEM TO AVOID FALSE POSITIVE DIAGNOSES

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Whole exome sequencing (WES) is being implemented by genomic diagnostics laboratories worldwide. However, next-generation sequencing remains error prone. While raw base-calling error rates are low, ~0.1%, rare variants identified for curation can have significantly higher error rates (3–6%). For instance, the investigation of de novo variants, that is, variants found in the proband and absent in both parents, will enrich for two types of false positives: genotype errors found only in the proband, and variants that were missed in one or both parents. With an average of 800 rare non-synonymous variants per individual, this means that up to ~50 sequencing artifacts could be confounding our analyses. On the contrary, true de novo variation is typically expected to be ~1 variant per individual. It is crucial that variant curators are able to identify sequencing artifacts that could, ultimately, lead to false positive diagnoses. Sequencing artifacts, commonly due to ambiguity in read alignment or PCR-associated errors, display a number of properties that can help us to distinguish them from the true variants. In this report, we will present interpretation of variant quality filters and genotype qualities to recognize potential false variants. Moreover, we will show the use of family information to aid in the calculation and interpretation of proband's genotypes. Finally, using genotype errors from trio analyses as a set of false positives, it will be shown how quality filters and other sequencing parameters, such as depth or allele balance, can be implemented in the filtering process to minimize the number of artifacts.

33. SESQUIZYGOTIC TWINNING: ANTENATAL DIAGNOSIS AND MOLECULAR SUPPORT FOR HUMAN PARTHENOGENESIS

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Sesquizygosis describes a multiple pregnancy that is an intermediate between monozygotic and dizygotic twins. The concept has been largely theoretical, with convincing molecular evidence in only one published case. In this report, we present a definitive case of mono-chorionic diamniotic twins who presented with gender discordance. Genotyping data is presented demonstrating the twins to be maternally identical, but sharing half their paternal genome, thereby making them 75% identical, or sesquizygotic. Genotyping of 968 dizygotic twin pairs for an existing repository suggests sesquizygosis to be a rare event. Finally, we conclude that parthenogenetic activation of the haploid oocyte is the initial step in the etiology of sesquizygosis.

34. UTILITY OF VARIANT SEGREGATION TESTING IN CLINICAL EXOME VARIANT INTERPRETATION

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Background: Segregation analysis in additional family members is often performed following singleton clinical exome analysis to aid clinical interpretation of classified variants. Here we present the results on the diagnostic and clinical utility of segregation testing following singleton clinical exome analysis within the VCGS Clinical Genomics Laboratory. *Methods:* Segregation testing was performed via Sanger sequencing of classified variants when a potential diagnostic or clinical benefit was identified in a multidisciplinary team meeting. Segregation test results were retrospectively assessed in clinical exome cases (January 2016–March 2017). *Results:* A total of 157 of the 265 clinical exome cases (59%) had variants identified for reporting (8% had pathogenic, 39% had likely pathogenic, 35% had VUS-3A, 11% had VUS-3B, 6% had VUS-3C classifications). Segregation testing was requested for 60 cases (to date, 34 completed). De novo status was confirmed in 18, compound heterozygous in seven, segregation with phenotype in two and suspected inheritance confirmed in three cases. Conversely, suspected inheritance was not confirmed in four cases. Importantly, the additional information gained from segregation testing increased variant classification in 18% of cases (five cases had VUS-3As reclassified as likely pathogenic, and a single case had a likely pathogenic reclassified as pathogenic), thus improving the diagnostic yield of clinical exome testing. *Discussion:* Segregation testing following singleton clinical exome analysis is valuable for variant interpretation and classification, and improves the diagnostic yield of clinical exome

testing. These data have the potential to inform funding body policy regarding segregation testing.

35. A CLASSICAL CASE OF ANDERSEN-TAWIL SYNDROME

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Background: Andersen-Tawil syndrome (ATS), also known as Long QT syndrome type 7, is an autosomal dominant disorder with cardiac and musculoskeletal manifestations. Most cases are due to mutations in *KCNJ2*. **Case Report:** We report on a 26-year-old lady with ATS confirmed on genetic testing. She initially presented with recurrent palpitations and documented bidirectional ventricular tachycardia (VT). Prolongation of the QT interval was noted on resting ECG. Transthoracic echocardiography and cardiac magnetic resonance imaging (MRI) revealed a structurally normal heart, and an exercise stress test showed ectopy and self-limiting bidirectional VT at rest that abated during exercise. Initially, other more common causes of bidirectional VT, including catecholaminergic polymorphic ventricular tachycardia (CPVT), were considered; however, our patient's exercise stress test result coupled with her phenotypic features led to the clinical diagnosis of ATS. Facial features are subtle in ATS; hypertelorism, low-set ears and micrognathia were present in our patient. Having initially suffered ongoing palpitations despite beta-blocker therapy, she has now been stabilized with a combination of atenolol and flecainide. Given her clinical presentation and investigation results lack high-risk features for sudden cardiac death (syncope, malignant arrhythmia with circulatory failure, family history of sudden cardiac death), an implantable cardiac defibrillator (ICD) has not been implanted. **Conclusion:** This case illustrates the importance of considering the diagnosis of ATS in patients with syncope, prolonged QT interval, ventricular arrhythmias and typical physical features. Risk stratification is paramount in guiding therapy to prevent sudden cardiac death due to arrhythmia.

36. IMPLEMENTATION AND CLINICAL EFFECTIVENESS OF A FAMILY HISTORY-DRIVEN RISK ASSESSMENT TOOL WITHIN PRIMARY CARE

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Background: Family health history (FHH) remains the strongest genetic predictor of disease risk in many conditions, yet is significantly under-utilized in routine risk assessment. We designed a patient-facing FHH-driven risk assessment tool, MeTree, with embedded education and clinical decision support (CDS) for evidence-based, guideline-directed, risk-stratified prevention strategies for 30 conditions. Here we report uptake and patients who meet criteria for non-routine preventive care (i.e., earlier or more intensive screening) and genetic counseling (GC). **Aims:** To evaluate implementation and clinical effectiveness of MeTree in real-world setting. **Methods/Design:** Implementation-effectiveness study. **Setting:** primary care clinics across 5 USA health systems. **Sample:** Adult patients with upcoming appointments and their providers (PCP). **Intervention:** MeTree. **Measures:** MeTree risk categorization, patient/provider surveys, EMR pull. **Primary outcome:** Implementation outcomes of uptake, adoption, and sustainability. **Secondary outcomes:** MeTree risk categorization. **Clinical care change post-intervention.** **Results:** Enrollment/consent (% of approached): 19 clinics (86%); 106 PCPs (79%); 2,383 patients (54%) of which 1,702 completed MeTree (71% of consented). Patient-participant demographics: age range 19–94 (mean 56, *SD* 14), 69% female,

and 85% Caucasian. MeTree recommended non-routine preventive actions for: 145 (12%) for breast cancer (women only); 285 (17%) for colon cancer; 775 (46%) for diabetes, 15 (1%) for liver diseases; 83 (5%) for inherited cardiomyopathies. MeTree recommended GC for inherited conditions for: 328 (19%). **Discussion:** We have demonstrated that MeTree is well received and quickly adopted by providers and patients. MeTree identifies a significant portion of the population at above-average risk who may benefit from more intensive screening and/or GC.

CYTOGENETICS

37. USE OF HIGH-DENSITY SINGLE NUCLEOTIDE POLYMORPHISM (SNP) ARRAYS FOR GENETIC DIAGNOSIS OF BECKWITH-WIEDEMANN SYNDROME

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Chromosomal microarray analysis (CMA) is now well established as a first-tier clinical diagnostic test to detect copy number variations across the human genome in several clinical settings. In addition, recent development of high-density SNP genotyping platforms revolutionized its potential to detect copy neutral genetic variations and thus allow the detection of copy-neutral loss or absence of heterozygosity, regions identical-by-descent, and uniparental disomy (UPD). As a result, SNP genotyping arrays now offer yet another valuable genotyping method. Beckwith-Wiedemann syndrome (BWS) is an imprinting disorder characterized by overgrowth, tumor predisposition and other congenital anomalies. It is caused by (epi)genetic alteration of one or more genes within the 11p15.5 imprinted gene cluster. Paternal UPD for 11p (patUPD11p), largely in a mosaic state, contributes to the etiology of ~20% of BWS cases. Current gold standard for the molecular diagnosis of BWS is the methylation-sensitive multiplex ligation-dependent probe amplification assay that is used to determine the methylation pattern for imprinting centres; IC1 and IC2. This assay can also be used to detect Silver-Russell syndrome (SRS) resulting from hypo-methylation of paternal IC1. Using this assay, up to 20–30% of clinically diagnosed BWS and SRS cases still remain genetically undiagnosed. For at least among cases with patUPD11p, this missed diagnosis is likely due to low-level somatic mosaicism for UPD11p. Here, we demonstrate that trio analysis using SNP arrays can be used as an alternative method for molecular diagnosis of BWS resulting from low-level mosaicism for patUPD11p.

38. PEDIATRIC APL WITH A VARIANT T(15;17) INVOLVING AN INSERTION AND AN INVERSION: A CASE REPORT

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Background: Acute promyelocytic leukaemia (APL) is characterized by the classical t(15;17)(q24;q21) and PML-RARA gene fusion. This type of leukaemia is infrequent in children. PML-RARA gene fusion can also arise by cryptic chromosome insertion, more complex rearrangements such as three-way translocations, or involve other partner genes that also disrupt RARA and form variant gene fusions. **Aim:** We describe a variant pediatric APL case with PML-RARA gene fusion generated from a likely insertion but appears to also involve a more complex inversion rearrangement of chromosome 17. **Method:** G-band karyotype, fluorescence in situ hybridisation and reverse-transcriptase polymerase chain reaction (RT-PCR) for PML-RARA fusion, and chromosome microarray analysis were performed to characterise the chromosome rearrangement. **Results:** Interphase

FISH showed three copies of the PML and RARA probes with only one gene fusion signal. Subsequent karyotyping showed an abnormal chromosome 17 that appeared to be a pericentromeric inversion; 46,XY,ins(17;15)(q21;q24q24)inv(17)(?q24?p12)[20]. Metaphase FISH showed a gene fusion signal but also a separate diminished 5' RARA signal on the der(17). RT-PCR demonstrated a chimeric PML-RARA fusion 'bcr3' transcript with PML exons 1–3 fused in-frame to RARA exon 3–7. CGH+SNP chromosome microarray showed no copy number imbalance. *Conclusion:* We describe a variant APL with PML inserted into RARA on the derivative chromosome 17, which also appears to be comprised of pericentric inversion. However, this rearrangement is likely to be more complex given the placement of the 5' RARA signal on the der(17). Since the PML-RARA transcript was detected, prognosis was not altered, and the patient remains in remission.

39. HEMICENTRIC INVERSION IN MAN? – A VERY RARE EVENT WITH UNKNOWN REPRODUCTIVE RISKS.

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We report the findings in a 37-year-old male with oligozoospermia sent to our laboratory for cytogenetic evaluation. GTG-banded chromosomes revealed a small inversion in one chromosome number 22. The inversion involved the centromeric region (q11.1) and proximal band q11.2. This was confirmed with C-banding, which showed that the centromere was split into two, forming a dicentric chromosome. FISH confirmed this finding, and showed that the HIRA locus was between the 2 centromeres. Microarray analysis showed no copy number changes in the region of the chromosome 22. There are very few reports in the literature of inversions with a breakpoint within the centromere. In plants it is called a hemicentric inversion. As they are so rare, it is difficult to determine whether it may have contributed to the patient's oligozoospermia. Some inversions can affect fertility. During meiosis, if recombination takes place between the centromeres, an isodicentric chromosome 22 could be produced. The result is an inv dup(22)(q11.2) which, when present as an ESAC, is the cause of cat eye syndrome (CES). A further complication is the presence of large (200-500kb) highly homologous chromosome-specific low copy repeats (LCR's) in 22q11.2, which are thought to predispose this region to aberrant recombination and subsequent duplication/deletion. An unequal exchange during meiosis in this patient might lead to deletion of HIRA, which causes VCFS/DGS, or duplication. There are a number of potential risks for this patient when undergoing IVF, and these are difficult to quantify due to the unique structure of this rearrangement.

40. A CASE OF ACUTE LYMPHOCYTIC LEUKEMIA (ALL) WITH MONOSOMY 9 AND AN ADDITIONAL PHILADELPHIA CHROMOSOME

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Background: Philadelphia chromosome (Ph) resulting in t(9;22) has been known as a common chromosomal abnormality in leukemic cells, particularly chronic myeloid leukemia (CML) and less frequently, acute lymphocytic leukemia (ALL). *Method:* Cytogenetic analysis was performed on a bone marrow from a 30-year-old male with relapsed precursor B cell ALL. FISH analysis for BCR-ABL1 fusion and the ASS gene and genome-wide 8x60K ISCA chromosome microarray analysis (CMA) was also performed. *Results:* An abnormal karyotype of 46,XY,-9,t(9;22)(q34;q11.2),+der(22)t(9;22)[13]/46,XY[2] was detected. FISH analysis showed three BCR-ABL1 fusion signals and a loss of ASS in 36/45 interphase nuclei indicating chromosome 9 loss.

Subsequent microarray analysis confirmed chromosome 9 loss and gain of Ph chromosome but also showed additional copy number abnormalities, including regions with homozygous deletions of IKZF1 (109kb), CDKN2A/2B (140kb), and part of RB1 (74kb). Microarray also found a subclonal deletion (14Mb) involving several genes within chromosome 11, bands q23.3 to q25. The ATM gene within chromosome band 11q22.3 was not involved. *Conclusions:* G-band Karyotype, FISH and CMA analysis detected the additional Ph chromosome and monosomy 9. CMA analysis also identified secondary chromosome changes consistent with relapsed ALL involving homozygous deletions of known tumor suppressor genes IKZF1, CDKN2A/2B and RB1. To our knowledge, this is the first ALL case reported with double Ph and monosomy 9. The clinical significance of the loss of chromosome 9 is currently unknown; however, the presence of BCR-ABL1 gene fusion and homozygous loss of known tumor suppressor genes suggests an unfavorable prognosis and high-risk disease.

41. THE USE OF MICROARRAY AND STANDARD CYTOGENETIC TECHNIQUES IN A SINGLE CASE WITH MULTIPLE MYELOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Advances in culturing and diagnostic methods have recently been made in the field of oncological cytogenetics. Microarray analysis has become a routine method for the analysis of specific oncological diseases such as chronic lymphocytic leukemia (CLL). However, in cases presenting with additional oncological disorders, several diagnostic methods are required to elucidate the findings. *Results:* We were presented with an 89-year-old man exhibiting bone marrow histology characteristics indicative of both CLL and multiple myeloma (MM). Several diagnostic tests were performed to confirm these findings cytogenetically. Microarray analysis performed on a B-cell enriched culture of the bone marrow revealed abnormalities consistent with that of CLL. A panel of FISH probes performed on a CD138+ plasma cell enriched culture of the bone marrow revealed abnormalities consistent with that of MM. Conventional analysis of the cultured bone marrow revealed complex abnormalities consistent with that of MM, while conventional analysis of the bone marrow culture containing B-cell mitogens had abnormalities consistent with CLL. This case highlights how these two diseases, established in different cell lines, required specific cytogenetic techniques in order to cultivate the cells specific to their respective diseases. *Conclusion:* This case demonstrates the necessity for the use of various cytogenetic techniques for cultivation of different cell types in order to make a successful diagnostic interpretation, particularly in the case of oncological diseases arising from diverse cell lineages. We recommend different culturing methods and cytogenetic techniques, including the standard conventional cytogenetic methods in conjunction with the more progressive microarray approach, in order to gain an accurate representation of oncological diseases of both B-cell and plasma cell origins.

42. G-BANDED CHROMOSOME ANALYSIS: VALUABLE RESOURCE AS ILLUSTRATED BY A PRENATAL CASE OF MOSAIC TETRASOMY 9P

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9p tetrasomy is a rare chromosomal imbalance defined by the presence of a supernumerary isochromosome involving the short arm of chromosome 9, or isodicentric chromosome that additionally includes 9q material. Prenatal diagnosis of mosaic or non-mosaic

tetrasomy 9p is uncommon. Here we present a prenatal case of mosaic tetrasomy 9p in a fetus with multiple abnormalities using CGH microarray where conventional karyotyping assisted in elucidating the nature of the imbalance. While microarray provides a significant advantage in terms of resolution, it has limited capacity to ascertain the cytogenetic mechanism of copy number changes identified.

GENETIC COUNSELING

43. WITHDRAWN

44. WITHDRAWN

45. EXPLORING THE EXPERIENCES AND SUPPORT NEEDS OF NON-CARRIER FATHERS OF CHILDREN WITH FRAGILE X SYNDROME

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Clinical features of children with fragile X syndrome (FXS) include developmental delay or intellectual disability and behavioral, emotional and specific learning challenges. Premutation carriers may present with fragile X-associated tremor/ataxia syndrome (FXTAS), fragile X-associated primary ovarian insufficiency (FXPOI), or increased anxiety and depression. The diagnosis of FXS in a child often reveals the premutation carrier status of their mother. The genetic counseling process may therefore focus on their information and support needs, without significant attention given to those of the non-carrier father. The aim of this research is to explore the experiences and support needs specific to non-carrier fathers of children diagnosed with FXS, an area which, to date, has not yet been investigated. Recruitment of English speaking, non-carrier fathers to participate in a semi-structured telephone interview is being facilitated through the NSW GOLD service and the Fragile X Association of Australia. Interviews are audio-recorded, transcribed verbatim, de-identified and coded using data management software NVivo11; coding concordance is being assessed by three independent coders. Thematic analysis is guided by the general inductive approach. Six participants have been interviewed to date. Preliminary themes identified include (1) 'The Mis-Diagnostic Journey', (2) 'Making Life Easier through Understanding — Yesterday, Today and Tomorrow', (3) 'The Path to a New Normal', and (4) 'Support — The Good, the Bad and the Ghastly'. The findings may inform the provision of more tailored genetic counseling support not only for fathers of children with FXS, but of other neuro-cognitive conditions.

46. EARLY ORIGINS, EPIGENETICS AND DISEASE: WHAT DO PARENTS WANT TO KNOW AND WOULD THEY INTERVENE?

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Epigenetics plays a part in many chronic diseases, which collectively contribute to an increasing burden on the healthcare system as their prevalence increase. The Developmental Origins of Health and Disease (DOHaD) hypothesis presents unique opportunities regarding the possibility of early life interventions to alter the epigenetic makeup of an individual, thereby modifying their risk for a variety of chronic diseases. While it is important to determine how we can prevent these chronic diseases, it is equally important

to understand how the layperson's knowledge and opinion of DOHaD and epigenetic concepts may influence their willingness to undertake interventions for themselves and their children to prevent chronic disease. Using an anonymous online survey, this study, which is currently in progress, aims to gain an understanding of parents' and the general public's knowledge and opinions relating to epigenetics, early life origins of chronic disease, disease risk testing in children, and the preventive options this may allow. Recruitment is mainly online, through Facebook and the Raising Children Network website, as well as in-person through Maternal and Child Health Centres. The survey, which takes approximately 30 mins to complete collects predominately quantitative data, with options for additional free text. We aim to collect approximately 200 questionnaires. In this exploratory study, data analysis will include mainly descriptive statistics of quantitative data and content analysis of free text data. This research will provide much needed information about the layperson's understanding and opinion of these important concepts, allowing health care professionals to better understand the needs of patients.

47. INCORPORATING NON-INVASIVE PRENATAL TESTING (NIPT) GENETIC COUNSELING INTO AN AUSTRALIAN PUBLIC HOSPITAL SETTING

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Non-invasive prenatal testing (NIPT) for fetal chromosomal abnormalities has been rapidly adopted into private obstetric practice in Australia since its introduction in 2013. Professional societies recommend that NIPT be accompanied by genetic counseling so that families can make informed reproductive choices. Currently, there are few clinics directly offering NIPT, and the associated pre- and post-test genetic counseling within the NSW public hospital system. At Royal Prince Alfred Hospital (RPAH) a genetic counselor-led NIPT clinic has been established since 2014 offering pre- and post-test genetic counseling to public patients. We report on the lessons learned from 3 years' experience and over 1,000 pregnant women seen through the NIPT clinic. Case examples are used to illustrate our robust workflows and the importance of pre- and post-test genetic counseling in our multidisciplinary model of care. Further to this, we will discuss our experience with the recently introduced expanded micro-deletion panels, including 22q11.2 deletion syndrome. The introduction of NIPT has brought new challenges to the prenatal care setting. Our work highlights that families and healthcare providers need appropriate support and education to ensure that this revolutionary new technology is utilized appropriately, allowing families to make informed reproductive choices.

48. ATTITUDES OF AUSTRALIAN WOMEN OR COUPLES AFFECTED BY MITOCHONDRIAL DISEASE TOWARD MITOCHONDRIAL REPLACEMENT THERAPY

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Background: Maternally inherited mitochondrial diseases are characterized by a broad spectrum of symptoms and severity. Although all children of an affected mother are at risk of inheriting the causative mutation, current prenatal testing technologies cannot always accurately determine the risk of a child developing a severe form of mitochondrial disease. Mitochondrial replacement therapy (MRT), utilizing donor egg cytoplasm through IVF, can greatly

reduce the risk that a couple will pass on a maternally inherited mitochondrial condition. At present, MRT is not available in Australia. *Aim:* To explore the views of maternally inherited mitochondrial mutation carriers and their partners regarding current reproductive options and MRT. *Methods:* Affected women attending the Neurogenetics clinic at Royal North Shore Hospital were sent recruitment packs and invited to participate in audio-taped semi-structured interviews. De-identified transcripts are being coded with concordance assessed by three independent coders. Themes are being identified by thematic analysis using an inductive approach. *Results:* 5/19 affected women consented to participate and 3/5 have been interviewed; recruitment is ongoing. Four emergent themes have been identified: (1) Perceived value: advantages and disadvantages; (2) Utility: limited currently available options, preservation of biological connection; (3) Access: legal and financial barriers, selection criteria; and (4) Awareness: highly knowledgeable cohort, need for public education, acknowledgment of stigma potential. *Significance:* Results to date indicate that MRT is perceived to be of real value to affected Australians and support revision of the current legal framework in Australia.

49. THE VICTORIAN ASHKENAZI JEWISH SECONDARY SCHOOL CARRIER SCREENING PROGRAM FOR TAY-SACHS DISEASE AND RELATED CONDITIONS

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There are a number of autosomal recessive conditions that are more common in the Ashkenazi Jewish population, including Tay Sachs disease (TSD). From 2003–2015, Austin Health and VCGS offered a funded genetic carrier screening program for Year 11 students attending the six Jewish secondary schools in Melbourne, Victoria. Screening was initially for Tay Sachs disease, and in 2008, funded screening for six other genetic conditions was introduced, with an eighth condition added in 2014. Over this 13-year period, 4,058 Year 11 students were screened, and 325 students were identified as carriers. Eleven of these students were carriers of two conditions, and one was a carrier of three conditions. The frequency of TSD carriers in this population from 2003–2007 was 1 in 33. Subsequently, the carrier frequency for all conditions screened from 2008 to 2015 increased to 1 in 8.5 students. Due to the rapid advances in screening technology, it is now possible to screen for carrier status for more than 100 genetic conditions. Consequently, funded carrier testing in the Jewish schools in Melbourne ceased in 2016, so individuals can consider being tested for more conditions nearer the time of commencing their own family. The focus is now on raising awareness of genetic carrier screening via secondary school education sessions, as well as informing and educating health professionals about the recommendations and availability of genetic carrier screening options for individuals of Ashkenazi Jewish ancestry.

50. FAMILY COMMUNICATION FOLLOWING A DIAGNOSIS OF MYOTONIC DYSTROPHY

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Background: Family communication about genetic information is pivotal to genetic health services. Unlike other medical information, genetic information can have important health and

reproductive implications for the wider family. Dissemination of genetic information to at-risk family members is frequently reported to be low. An ethical tension therefore arises in genetic counseling between the concepts of individual patient autonomy and confidentiality, and beneficence to at-risk relatives. It is important that we understand family communication processes so that we can assist families to communicate genetic information. Review of the literature identified no studies exploring this issue in the context of myotonic dystrophy. A recent prevalence and impact study, MD Prev, ascertained individuals diagnosed with genetic muscle disorders in New Zealand (NZ). Families with type 1 myotonic dystrophy (DM1) who agreed to further follow-up have been identified and invited to discuss their communication patterns. *Methods:* This exploratory study is taking place across multiple sites in NZ. Between April and July 2017, 12–20 individuals over the age of 18 years, who have either received a diagnosis of DM1, or who are parents who have received a diagnosis of DM1 for their child, are being interviewed. Participants are being recruited through the MD Prev study. Interviews are semi-structured, and explore individuals' experiences receiving a diagnosis of DM1, and how they communicate genetic information with their relatives. All interviews will be recorded, transcribed, and analyzed using thematic analysis. *Results and discussion:* Data collection is expected to be completed in July. Results will be presented.

51. LEXIGENE (®): AN ONLINE ENGLISH–FRENCH–SPANISH LEXICON OF TERMS RELATED TO GENETIC COUNSELING

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To facilitate the provision of genetic services in the three most commonly spoken languages in North America and to contribute to the development of the genetic counseling profession, an English–French–Spanish lexicon of terms was created by genetic counselors for the specific use of genetic counseling. Trainees in bilingual genetic counseling training programs, as well as francophones and hispanophones who have access to the mainly anglophone scientific literature, are in particular need of such a tool. Prior to the creation of Lexigene(®), no French/English glossaries or lexicons with terms related to genetic counseling were available. Similarly, although a Spanish/English glossary was created in the 1990s, the medical genetics terminology had not been updated in almost 20 years. The original French–English Lexigene(®) was funded through the Canadian Association of Genetic Counselors and was published online in 2011. In 2016, the National Society of Genetic Counselors' Audrey Heimler Special Project Award was given to include Spanish. This trilingual website, www.lexigene.com, allows an individual to search for genetics-related terms in either English, French, or Spanish and find the equivalent term in the other language. This online tool boasts around 3,600 translated terms, with more being added regularly. Lexigene(®) will be used by genetic counselors, genetic counseling trainees, geneticists, medical interpreters, and others who work in the field of genetics in English, Spanish, and French in a bilingual setting or on an international scale.

52. GENETIC COUNSELING CERTIFICATION IN AUSTRALASIA: THE CURRENT LANDSCAPE

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The training of genetic counselors is a two-step process: the acquisition of theoretical knowledge, currently via a master's degree, followed by a clinical certification process. When genetic counseling certification was introduced in Australasia in 1990, the process involved demonstration of clinical skills via submission of 20 long case reports, as well as continuing education and supervision reports over a minimum 2-year period. In 2010, guidelines for a revised certification process were released. These guidelines detailed a new set of criteria and submission requirements, termed a portfolio, to address the increasing complexity of genetic knowledge and achieve equivalency in certification standards with overseas programs. In addition, there was a move toward more varied assessment methods that include two reflective skills assessments, five long case reports, a logbook of cases, and a publication or literature review, as well as continuing education and supervision reports. Since the introduction of the revised guidelines, a number of genetic counselors have now completed the new certification process, and anonymous feedback has been sought to help evaluate and improve the process. This presentation will outline the characteristics of candidates currently undertaking and having completed the new certification process, as well as a discussion of feedback received from genetic counselors already certified by the new process.

53. A NOVEL OPPORTUNITY FOR UNDERGRADUATE MOLECULAR BIOLOGY STUDENTS TO EXPERIENCE THE FIELD OF GENETIC COUNSELING

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The demand for qualified genetic counselors is expected to expand. Subsequently, there is a need for undergraduate university programs to stimulate interest in the field and give prospective students exposure to a genetic services prior to admission into a Master of Genetic Counseling course. This overview presents a joint program between the ACT Genetic Service and the Australian National University developed in 2012, with the aim of offering undergraduate students studying molecular genetics exposure to the growing field of genetic counseling. The program includes a lecture series presented by an ACT genetic counselor in a third-year human genetics course within the Australian National University and 40 hours of work experience at the ACT Genetic Service, in which students sit in on genetic counselor and clinical geneticist consultations. Students learn about the process of genetic counseling, including the use of a genetic database and pedigree drawing program. Outside of the genetic clinic, students participate in genetic counselor-led tutorials that further explore ethical, clinical, and communication issues that may have arisen during the work experience. Student assessment includes a 5,000-word thesis on a topic of choice from their work experience, a 15-minute presentation and a reflection piece. The program has maintained extremely high satisfaction rates with students and has been successful in creating awareness and interest in the field of genetic counseling.

54. IS AN INFORMATIVE WEBINAR ENOUGH TO PROVIDE INFORMED CONSENT FOR PGS?

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Since the introduction of Next Generation Sequencing technology to screen for aneuploidy, the number of patients referred for preimplantation genetic screening (PGS) has drastically increased. PGS volumes have increased by 50% in 2015 and 25% in 2016 and represents ~80% of the clinical workload at Monash IVF. Historically, patients were offered a 30-minute appointment with a genetic counselor. The delivery format of PGS information needed to change to accommodate growing demand; as such, an informative webinar was developed to deliver pertinent information to patients considering PGS. This study aimed to evaluate if a webinar is an efficient and adequate way to inform Monash IVF patients. The PGS webinar could be accessed at any time and viewed as often as patients wished. The webinar contained key information relating to the embryo biopsy procedure, the PGS process, the risks, limitations, and the potential outcomes. Patients were given the opportunity to speak with a genetic counselor if they had further questions regarding PGS after viewing the webinar. Patients were asked to complete a questionnaire containing 16 questions about the webinar, its format and the information it contained. Here we will present the data obtained from this survey and review patient responses. Results from this study will be used to determine the most efficient and effective way to provide information to Monash IVF PGS patients. Survey responses will be used to modify the Monash IVF genetic counseling program to offer the best practice for patients using the resources available.

55. A CASE OF TWO APPARENTLY DE NOVO MUTATIONS IN THE DYSTROPHIN GENE IN A SINGLE SIBSHIP

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Duchenne/Becker muscular dystrophy (DMD/BMD), are X-linked recessive genetic neuromuscular disorders, which typically present with gradual progressive muscle weakness. Both conditions are caused by mutations of the Dystrophin gene which is located at Xp21.2. We present an atypical genealogy in which two sisters have different mutations in the dystrophin gene. *Case presentation:* We describe a 31-year-old pregnant woman, who presented at 16 weeks' gestation requesting carrier testing for DMD. Her nephew had recently been clinically diagnosed with DMD. The familial mutation in the Dystrophin gene was unknown in the proband at the time. Molecular analysis of the pregnant woman demonstrated a heterozygous deletion of exons 14–32 of the dystrophin gene. This result is consistent with the patient being a carrier of Becker muscular dystrophy. Her male fetus was also found to have a heterozygous deletion of exons 14–32 of the dystrophin gene. Molecular testing of the proband later revealed an out-of-frame pathogenic variant in the Dystrophin gene, which was consistent with his clinical diagnosis of DMD. Molecular testing of the proband's mother identified the same out of frame pathogenic variant. Subsequent cascade testing in the two female siblings and their mother were all normal, indicating that it was most likely both mutations were de novo in the sisters. *Conclusions:* The present case report helps to better understand the complexities in molecular testing of the Dystrophin gene. Had molecular testing occurred in the proband first, the carrier status of BMD in our patient would have been overlooked.

56. THE GENETIC INFORMATION NEEDS OF PEOPLE WHO ARE ADOPTED: ADOPTEE PERSPECTIVES

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Background: People who are adopted often have limited access to family health history. Little is known about how this impacts on adoptees. Anecdotal reports suggest people who are adopted access direct-to-consumer testing to gain information about their inherited disease risks. As public interest regarding genetic health risks and disease prevention rises, people who are adopted may be increasingly presenting to genetics services. Uncovering the implications of limited knowledge of family history on adoptees is key in providing appropriate genetic counseling to this group. **Aim:** The study aims to explore the experiences of adoptees in regard to family health history information and genetics. **Methods:** This is a qualitative exploratory study that will take a phenomenological approach. Data collection will comprise semi-structured interviews with people who are adopted regarding their family health history and genetic information needs. A stratified purposeful sampling approach is taken to gain a wide range of perspectives. Recruitment is being carried out through adoption support groups and in the general public. Interviews will be transcribed verbatim, coded, and analyzed using thematic analysis. **Results:** Early findings suggest a range of complex issues facing adoptees with limited family health history information. Interviews with participants are ongoing with the data collection phase anticipated to conclude in July. **Discussion:** Through insight into the experiences of people who are adopted in relation to their knowledge of family health history and genetic information needs, the study hopes to help inform genetic health professionals about how to best assist adopted clients in clinical settings.

57. NON-INVASIVE PRENATAL TESTING FOR SEX CHROMOSOME ANEUPLOIDY: EXPLORING THE EXPERIENCES OF WOMEN AND THEIR PARTNERS

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Background: Non-invasive prenatal testing (NIPT) is an optional screening test, available from 10-weeks gestation, for the identification of pregnancies with an increased chance of common trisomies and, more recently, sex chromosome aneuploidy (SCA). Little is currently known about women and their partners' receptivity to screening for SCA, or their experience of receiving a high-risk result for SCA through NIPT. **Aim:** This qualitative study aims to gain an understanding of the experiences of women and their partners who have received a high-risk result for SCA from NIPT in Victoria Australia. **Methods:** Up to 15 women and their partners will be recruited through Victorian Clinical Genetics Services and Monash Ultrasound for Women. Women who have received a high-risk result for SCA through NIPT at least 12 months prior, and had genetic counseling following the result, will be identified through clinical records. A letter will be sent inviting women and their partners to participate in an in-depth semi-structured interview. Interviews will be transcribed verbatim and thematic analysis will be applied to identify common themes of importance to the participants. **Results:** We anticipate that this study will provide novel insight into how some women and their partners interpret and make meaning

from these results, the emotional impact of receiving this information, and decision making around diagnostic testing. Results are expected to be available from June onwards. **Conclusion:** The findings of this study may provide considerations for the future offering and reporting of SCA through NIPT, and may inform pre- and post-test genetic counseling practice.

58. THE GENETIC INFORMATION NEEDS OF PEOPLE WHO ARE ADOPTED: PROFESSIONAL PERSPECTIVES

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Background: Family history has long been considered an important tool in determining an individual's risks of some genetic conditions. Adoptees often have limited knowledge of their family history. The clinical and psychosocial implications of this, as well as the genetic counseling strategies employed by genetic health professionals to support these clients, have not been explored. **Aim:** The purpose of this study is to explore the experiences of genetic counselors and clinical geneticists when counseling adoptees who have limited knowledge of their family history. **Methods:** This is mixed-methods study comprising quantitative and qualitative data collection. A short survey will be conducted of members of the Australasian Society of Genetic Counsellors (ASGC) and Australasian Association of Clinical Geneticists (AACG) regardless of whether they have seen an adopted client or not. Statistical methods will be used to analyze the data. The survey data will inform the qualitative stage, including recruitment of professionals who have worked with an adopted client, for semi-structured interviews. Interviews will be transcribed verbatim, coded, and analyzed using thematic analysis. **Results:** The study is ongoing with the data collection anticipated to be completed by August 2017. Early findings suggest that there is little training given to genetic health professionals in relation to adoption. **Discussion:** By collecting data on the prevalence of adopted clients in the genetics setting and exploring the experiences of professionals with adoptees, the study hopes to inform clinical practice and develop recommendations for working with clients who have limited knowledge of their family history.

59. PSYCHOLOGICAL ADAPTATION TO GENETIC INFORMATION AMONG FIRST-DEGREE RELATIVES FOLLOWING SUDDEN CARDIAC DEATH IN THE YOUNG

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Background: A high prevalence of posttraumatic stress and prolonged complicated grief has been reported in family members following the sudden cardiac death (SCD) of a young person. We sought to determine the impact of postmortem (PM) genetic test results for family members after the SCD of a young relative. **Methods:** First-degree relatives who had experienced the SCD of a young family member and where PM genetic testing was undertaken were invited to participate in a survey comprised of psychosocial validated scales and exploratory questions. **Results:** Seventeen surveys have been returned to date (36 approached, response rate 47%, mean respondent age 5 ± 12 years, 24% male). Mean age of the decedent was 21 ± 9 years and the mean time since death 8 ± 7 years. Thirteen (76%) respondents received an uncertain result (variant of unknown significance or indeterminate result) following PM genetic testing and four (24%) received a certain result (likely pathogenic,

LP, or pathogenic, P). Psychological adaptation to genetic information scale indicated less certainty (perception of accurate knowledge of the disease) for family members who received an uncertain result compared to those with a certain LP/P result (4.22 ± 1.2 versus 5.52 ± 0.4 , $p = .04$). Posttraumatic stress symptoms were reported by eight participants (62%) with uncertain and one participant (25%) with certain results ($p = .21$). *Discussion:* Further exploration of the impact of PM genetic testing on psychological wellbeing after a SCD may ultimately help to improve the clinical care offered to families in the future.

60. THE PATIENT EXPERIENCE OF FAMILIAL MOTOR NEURONE DISEASE: A QUALITATIVE STUDY

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Background: Preventing and reducing incidence of amyotrophic lateral sclerosis (ALS), a motor neurone disease, is only possible in families with a known pathogenic ALS gene variant, through access to reproductive options that prevent variants being passed on to future generations. Uptake of this option is low, with little known about how individuals from familial ALS (FALS) families decide whether to have genetic counseling, testing, and pursue reproductive options. *Research question:* What are the barriers and facilitators to genetic counseling and testing for FALS in Australia? *Methods:* This 12-month mixed-methods study includes qualitative in-depth interviews with 30 Australian individuals from FALS families to explore their experience of FALS and the factors that influenced their decisions about genetic testing options. Data analysis is conducted using a generalized inductive approach and independent parallel coding. *Results:* To date, 16 interviews have been completed. Early results highlight that unique factors underlie each participants' decision-making about the testing options, and this is influenced by life stage, time, attitudes to FALS, and reproductive options. Facilitators of predictive testing include the need for information for children or family planning, time to be psychologically prepared or alter life's priorities. Barriers include no currently available preventative options for mutation carriers and the possible negative psychological impact of testing. These barriers could also be facilitators for participants considering reproductive testing. *Conclusion:* The results will provide greater insight into genetic counseling and reproductive decision-making for FALS, and contribute toward best-practice guidelines for management of FALS for both genetics and neurology communities.

61. CHOICE IN GENETICS CONSULTATIONS: FLEXIBILITY AND ACCESSIBILITY IN REGIONAL GENETICS SERVICES

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Background: Most genetics services in Australia are based on major cities. A number of these services provide outreach clinics to regional centers but there can be practical and financial issues for people that make it difficult to access these services. To our knowledge, this is the first study in Australia to explore both health professional and patient views on the incorporation of telegenetics into genetic counseling consultations in general genetics services in regional areas. Telegenetics can include telehealth/telemedicine, that is, conducting a health consultation via video conferencing, telephone consultations, and other remote methods of communica-

tion; for example, email or online resources. *Aim:* This qualitative research study aims to explore the views of both health professionals and clients of genetic clinics on the way genetics health services are delivered in regional areas and how these services can be more flexible and easier to access. *Methods:* A qualitative approach will be employed to explore the views of health professionals, both with and without direct experience of telegenetics, and patients of the Victorian Clinical Genetics Service on the use of communication technologies in consultations. Co-coded data will undergo thematic and content analysis using a constant comparative approach. *Results:* Three focus groups consisting of health professionals are being conducted in April and May and patients have been invited to participate in telephone interviews. Preliminary data will be presented. *Conclusion:* This information is important in understanding whether we are providing optimal genetics services to meet the needs of people in rural and regional areas.

62. WITHDRAWN

63. A SURVEY OF THE AUSTRALASIAN GENETIC COUNSELOR WORKPLACE: 15 YEARS ON

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National and international discussion highlights the importance of the genetic counseling workforce. This study therefore aimed to establish a snapshot of the current Australasian genetic counseling workforce and workplace and explore changes over the last 15 years. Invitations to participate in an anonymous online survey (RedCAP) were disseminated via genetic counselor listservs and promotion at relevant meetings. The survey was a repeat of that by James et al. (2003), with additional questions relevant to current and future practice. All 111 respondents to date reported that they are employed as a genetic counselor. Preliminary analysis shows respondents work in all states, territories, and New Zealand in traditional public genetics services, subspecialties, private practice, and other settings; 44% employed for >5 years in current setting. Compared to 2002, more genetic counselors working in research and private practice completed a survey; 55% work full time. Qualifications include Graduate Diploma (28%) and Masters (56%); and 38% are HGSA certified and 56% in training. Respondents reported increases in workload (85%) and changes in roles (76%), such as use of genome databases (~70%) and undertaking variant interpretation (~65%). Free text comments include 'more autonomy/responsibility'; 'manage increased complexity in information'; and 'implement new technologies'. Overall, 24% have considered changing roles, including decreasing their clinical contact. HGSA certification was valued, though lack of career path and level of salary/awards remain a concern. Analysis and recruitment is continuing. The findings will inform development of the profession, future workforce planning, and state and federal health policies related to genetic counseling service provision.

64. IDENTIFICATION OF A PTEN MUTATION IN A 3-YEAR-OLD BOY — THE AFTERMATH

Gabrielle Reid

Genetic Services of Western Australia, Perth, WA, Australia

A 3-year-old boy with macrocephaly and subtle coordination concerns was seen by the pediatric team at Genetic Services of Western Australia. Subsequent diagnostic testing identified a mutation in the PTEN gene. This presentation will review hamartoma tumor

syndrome (PHTS), under which there are a number of subcategories corresponding to the various clinical features that can present. Importantly, people with PHTS have a higher risk of developing benign (non-cancerous) and cancerous tumors. For women who carry a PTEN gene fault, there is an increased risk of developing breast and endometrial cancer, and for both men and women with a PTEN gene fault, there is an increased risk of bowel polyps, thyroid, and renal cancer. The challenges faced in the provision of genetic counseling for multiple members of this boy's family will be presented. Faced with a new diagnosis and potential threats regarding risk of cancer in their son, this boy's parents did not want to immediately proceed to testing in themselves. An ethical dilemma surfaced when the boy's maternal grandparents were independently referred to discuss the option of predictive genetic testing in the absence of their daughter being tested. The genetic counseling undertaken to explore the underlying adamant drive for testing in one, compared with the anxiety and reluctance to be tested in the other, will be presented and discussed.

65. IS THERE A ROLE FOR GENETIC COUNSELORS IN PRENATAL PATERNITY TESTING?

Kate Riley

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The role of genetic counselors in prenatal paternity testing has not been widely studied in the literature. In South Australia, the genetic counselors of the state's public sector clinical genetics service are the primary contact point for women seeking information and testing. This provided the opportunity to review all prenatal paternity testing performed in the state over a 13-year period and to consider the role of the genetic counselor. We explored the reasons why women requested prenatal paternity testing and whether the genetic counselor was an appropriate health professional to facilitate this testing. The study had two parts, an audit of the clinical genetics files of 160 women who requested prenatal paternity testing between March 2001 and March 2014, and qualitative interviews of genetic counselors, clinical geneticists, obstetricians, and social workers. The audit determined that in 69.9% of cases, the long-term partner was the father of the pregnancy, for 23.7% the short-term or other partner was the father. For 45.5% of women whose long-term partner was excluded as the father, the women chose to have a termination of pregnancy. Fourteen health professionals participated in the qualitative interviews. The results yielded five major themes: accessibility of testing, role of the genetic counselor, social and relationship issues, decision making in pregnancy, and emotional issues to facilitate prenatal paternity testing. Genetic counselors did not view their role as significantly different from a request for prenatal testing for another indication.

66. BECOMING A LABORATORY GENETIC COUNSELOR IN AUSTRALIA: HOW DO THESE ROLES INFORM OUR PROFESSIONAL FUTURE?

Mary-Anne Young and Skye McKay

Genome.One, Sydney, NSW, Australia

Background: The rapid development and uptake of genomic technology is significantly impacting a broad spectrum of health care domains, including the provision of genetic counseling. Genetic counselors in the United States have transitioned through a period of practice evolution and have defined a new specialty stream termed 'laboratory genetic counselor'. Although the laboratory genetic counselor role was initially considered 'non-traditional', this expanding discipline has become an integral part of the American genetic counseling workforce. **Australian context:** While the genetic counseling profession is still relatively young in Australia, we have previously resolved contentious and progressive issues, including

cancer genetic counselor specialization and working in private practice. With the genomic era well and truly upon us, Australian genetic counselors are currently facing new ethical and practical challenges around best-practice models of care. We have the opportunity to learn from the experiences of the United States and shape the role of laboratory genetic counselors to suit Australian practice. The Genome.One genetic counselors are prime positioned to consider the opportunities and challenges encountered when transitioning to 'laboratory' genetic counseling roles. Specific topics to be explored include the need for prior clinical experience, autonomy, supervision, and working in the private sector. This reflective presentation aims to contribute to the discussions around this exciting period of genetic counseling professional growth.

67. GENETIC COUNSELING FOR A FRAGILE X MALE WITH AN UN-METHYLATED, FULL MUTATION TRINUCLEOTIDE REPEAT

Erin Macaulay¹, Tarn Donald², and Kelly Sullivan¹

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Fragile X syndrome (FXS) is a genetic condition leading to a deficiency in the Fragile X Mental Retardation 1 (FMR1) protein as a result of a trinucleotide repeat (CGG) expansion in the promoter region of the FMR1 gene. The CGG repeat size in the FMR1 gene can inform the clinical symptoms experienced. An expanded repeat size of >200 would typically result in hyper methylation and therefore transcriptional silencing of the FMR1 gene. Recently, a male from a known FXS family has been found to carry an unmethylated FMR1 gene with a repeat size of >200. He is not clinically affected by FXS. This case study looks to discuss the possible clinical symptoms this male may experience due to his rare epigenotype and the implications for genetic counseling. Fragile X-associated tremor/ataxia syndrome (FXTAS) is a possible clinical symptom in an unmethylated full mutation carrier due to the elevated levels of the FMR1 mRNA. The genetic counseling implications for this case include a lack of knowledge of the possible clinical symptoms individuals may face. This case highlights issues of informed consent as the possibility of a full mutation carrier with an unmethylated FMR1 gene was not discussed with the patient and was not an expected result. There is a gap in the FXS genetic counseling guidelines for this type of result. This case study is presented to make genetic counselors aware of this outcome as a possibility and add to the small body of literature about unmethylated full mutations.

GENETIC EPIDEMIOLOGY

68. MOLECULAR DIAGNOSIS OF CHARCOT MARIE TOOTH DISEASE IN AUCKLAND, NEW ZEALAND

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Background: Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of genetic disorders characterized by sensory and/or motor neuropathy. Little is known about its prevalence. **Aims:** The Impact CMT study is a regional population-based study that aimed to determine the prevalence of CMT in adults and children in the Greater Auckland Region of New Zealand. **Methods:** Multiple sources of case ascertainment were utilized to identify people living with a diagnosis of Charcot-Marie-Tooth disease on June 1, 2016. Cases were verified against medical records and details of whether a genetic test had been completed and the result were extracted for all identified cases. **Results:** More than 200 cases of CMT were

identified. The age range was less than 1-year old through to 94 years of age, with mean age 44.5 years (*SD* 22.93). A fifth of the cohort was aged under 16 years. Half of the cohort was female. Three-quarters of those ascertained identified as NZ European. Overall, half of all individuals with Charcot-Marie-Tooth disease living within the greater Auckland region of New Zealand had a molecular diagnosis. *Discussion:* The proportion of individuals with a molecular diagnosis varied according to several factors, the main one being subtype of Charcot-Marie-Tooth, with the majority of people diagnosed with CMT1A and HNPP having a molecular diagnosis, whereas people with other types of CMT less likely to have a molecular diagnosis. Factors such as age and ethnicity on rates of molecular diagnosis will be examined.

GENETIC EDUCATION

69. THE CHEMOPREVENTATIVE EFFECT OF ASPIRIN IN LYNCH SYNDROME: DEVELOPMENT AND EVALUATION OF AN EDUCATIONAL LEAFLET

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Background: Carriers of germline mutations in mismatch repair genes associated with Lynch syndrome are at increased risk of developing colorectal, endometrial, ovarian, and other cancers. There is now good evidence that daily consumption of aspirin can reduce the cancer risk in these individuals. However, there are no educational resources to inform them of the chemopreventative effects of aspirin or to support decision making for those considering this strategy. *Aim:* To develop an educational leaflet to inform people with Lynch syndrome about the use of aspirin to reduce their colorectal cancer risk. *Methods:* The leaflet's content describing the risks and benefits of using aspirin was developed with experts involved in Lynch syndrome. Two health literacy measures — Flesch–Kincaid readability and Flesch reading ease score — guided the content presentation to sixth-grade reading level. One hundred ninety seven Lynch syndrome carriers, aged 18 years and over and proficient in English, recruited through the Parkville Integrated Familial Cancer Centre, Royal Melbourne Hospital, will be invited to participate in the resource evaluation. The hard-copy self-administered questionnaire is short and purposely designed, assessing content, and clarity (13 items), satisfaction with the length, relevance, and visual appeal of the resource, as well as understanding (13 Likert-type items). *Discussion and conclusion:* The results of this study will be integral to guiding improvements to the information resource and may result in the production of a widely distributed educational leaflet. Such a resource will be useful for patient education and as an aid to discussion between patients and their health care professionals.

70. NEW ACRONYMS FOR EPONYMOUS SYNDROMES IN CLINICAL GENETICS

Matthew Regan and Matthew Hunter
Monash Health, Clayton, Australia

A number of genetic syndromes are named after an acronym based on the common features, that is, CHARGE syndrome, VACTERL association, and MELAS. Acronyms exist on the internet for a number of common conditions such as 'my CHILD HAS PROBLEM' from Down syndrome, 'FELTERS' for Klinefelter syndrome, and 'CLOWNS' for Turner syndrome. Clinical genetics has a large num-

ber of eponymous syndromes and we have made new acronyms for a number of these using the following rules: (1) common in clinical genetics, outlined in the RACP *Clinical Genetics Advanced Trainee Handbook* or in the *Oxford Desk Reference — Clinical Genetics*; (2) use the syndrome or the gene. For Rubenstein Taybi our acronym is CREBBP — Columella low, Retardation, Eyelashes long, Broad thumb/hallus, Brows arched, and Palate elevated; Avoid re-inventing acronyms, avoid 'ABCDE...'; (3) include classic triads. For Aicardia syndrome our acronym is AICARDIA — *Agenesis of corpus callosum, *Infantile spasm, Coloboma, Atonia (muscle weakness), *Retinal lacunae, Denovo, Intracranial ventriculomegaly, Annihilates males (* = classic triad); (4) include complex scoring systems in the acronym. For example, the Ghent score in Marfan syndrome MARFANS — MVP Myopia, Arachnodactyly (thumb and wrist sign), Ratios (arm span to height and US:LS), Facial features Foot deformity, Asymmetry of chest (pectus carinatum/excavatum), pNeumothorax arm extension, Scoliosis, and Striae. Other new acronyms include ALAGILLE, ALPORT; ALSTROMS ALMS1, ANGELMAN, BECKWITH, COCKAYANES, coffin LOWRYS, COFFIN siris, COSTELLO, CROUZON, CYTOMEGALOVIRUS, ECTODERMAL, FABRYS, FANCONI, FRAGILE X; HOLT ORAM; KABUKI; MUCOPOLYSACCHARIDOSIS; NOONAN; PATAU; PRADER; russell SILVER; SIMPSON G BH; SMITH LEMLI; GIGANTISM (Sotos); USHER; WAARDENBURG.

GENOMICS

71. PHARMACOGENOMICS PROFILING USING CLINICAL WHOLE GENOME SEQUENCE DATA

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Background: Pharmacogenomics (PGx) is the study of how variants in the genome affect responses to medication. PGx testing has been largely constrained to interrogating a small number of SNPs, but as massively parallel sequencing becomes more commonplace, we envisage PGx as one component of a clinical whole genome report. Here we report high-resolution PGx profiling using whole genome sequencing (WGS) data. *Methods:* We developed a method for determining PGx star alleles (haplotypes) from WGS variant calls and PharmGKB translation tables. In a pilot study at our NATA/RCPA clinically accredited WGS laboratory, the method was applied to 22 genes in 13 individuals referred for WGS. Results were compared to conventional, PCR-based laboratory testing from a CAP/CLIA clinically accredited PGx laboratory. *Results:* There was a high level (96%) of concordance of WGS-based results with genotype results from the PGx laboratory. One sample was reported by the PGx laboratory to have a CYP2D6 allele with a whole gene duplication, and this was successfully predicted from the WGS data. The only discrepancies were that in several samples, the WGS method found two equally likely genotypes in CYP2D6 or CYP2B6, but only one of these was reported by the PGx laboratory. *Conclusion:* Our results show that using WGS data, it is possible to emulate a commercial test from a PGx laboratory. Larger scale validation is required, particularly of the gene CYP2D6 which is subject to extensive variation. WGS has the potential to reveal novel or rare genotypes which are not detectable by current testing methods.

72. DEVELOPMENT OF KAPA HYPER PCR-FREE WGS WORKFLOW IN GENOME.ONE

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Genome.One's sequencing service provides research and clinical whole genome at >30× coverage on the Illumina HiSeq × Ten system. When sufficient amounts of genomic DNA are available, the PCR-Free method improves coverage and uniformity by reducing bias and gaps, and therefore significantly improves the sensitivity and specificity when calling indels and CNVs, particularly in GC-rich regions. The demand for PCR-free WGS is growing rapidly; however, some clients are not able to provide 1 µg of high-quality genomic DNA as required in the Illumina SeqLab PCR-free workflow. Thus, an alternative PCR-free workflow is needed to meet client requirements. We developed a rapid PCR-free WGS workflow on HiSeq × Ten using KAPA Hyper kits. In comparison to the Illumina TruSeq PCR-free method, the KAPA Hyper PCR-free workflow has shorter turn-around time and hands-on time and requires lower quantities of input DNA (500 ng). The analysis of sequencing data shows that KAPA Hyper PCR-free workflow provides better specificity and reproducibility and comparable sensitivity in detecting variants. Furthermore, to facilitate high throughput DNA library construction, we modified existing SeqLab components and coded new scripts for Hamilton Microlab STAR and Clarity LIMS to develop an automated workflow. Automation of the KAPA Hyper PCR-free workflow reduces variation and minimizes failure. The faster high throughput library preparation, coupled with the reduced input DNA requirements, provides advantages for processing both research and clinical samples for WGS on the HiSeq × Ten system.

73. MOSAIC RYR2 MUTATION IDENTIFIED IN A CHILDHOOD-ONSET CARDIOMYOPATHY

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Somatic mosaicism occurs when a genetic variation occurs after fertilization and propagates in the cell lineages as an embryo develops. Mosaic variation is increasingly recognized to play a causal role in a variety of human diseases. A recent study has shown that early somatic mosaicism in an infant was a rare cause of long-QT syndrome [Priest, *PNAS*, 2016]. We present a case of somatic mosaicism in a 12-year-old boy presenting with cardiomyopathy, multiple arrhythmias, and cardiac remodeling. Whole exome and cardiac panel analysis were performed focusing on the cardiomyopathy and arrhythmia genes. A novel variant was identified in the cardiac ryanodine receptor gene (RyR2). Whole exome analysis indicated that this variant was the only likely pathogenic variant and cardiac gene panel analysis indicated that the variant was mosaic at a level of ~22%, evident on both blood and cardiac tissue. RyR2 is the major calcium-ion release channel of the sarcoplasmic reticulum and plays an essential role in excitation — contraction coupling and calcium-ion homeostasis [Tang, *Circ Res*, 2012]. Mutations in RyR2 usually cause arrhythmia conditions in structurally normal hearts. The mechanism for RyR2-associated cardiomyopathies remains unknown. However, a recent study suggests that abnormal cytosolic calcium-ion movement may be associated with cardiomyopathies and trigger the cardiac remodeling associated with cardiomyopathies [Tang, 2012]. Further clinical evidence to assess the impact of the RyR2 variant and segregation in family and different tissues reflecting the variant mosaicism will be presented. Detection of mosaic variants may be an important follow-up analysis in patients without genetic diagnoses.

74. EVALUATION OF THE WHOLE EXOME SEQUENCING ON BGISEQ-500 PLATFORM

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Next generation sequencing technology application, especially the WES, drive the research application and clinical application into a dramatic industrial period. The BGISEQ-500 based on DNA Nanoballs (DNB), patterned array and combinatorial Probe-Anchor Synthesis (cPAS) sequencing technology have published as a new sequencing platform. In this study, BGISEQ-500 WES data was evaluated and also been compared with the Illumina platform data. A total of 1 µg NA12878 gDNA was applied to the WES library construction following the MGIEasy™ Exome Library Prep Kit V1 and Exome Capture V4 Universal Kit protocol with more than three replicates and sequenced on the BGISEQ-500 with paired end (PE) 50 bp, 100 bp, and 150 bp strategy. Raw data were filtered and mapped to the reference sequence (hg19). Capture efficiency, duplication rate, and chimerical rate were calculated based on mapped reads. Meanwhile, SNP and Indel detection were also analyzed to evaluate different sequencing read length influence; long PE reads data provide a 5% to 15% higher capture rate, 3% to 10% lower duplicate rate and 0.1% to 1.5% lower chimerical rate than the short one, and the SNP sensitivity rate dropped <0.3%. Gradient coverage depth, 20×, 40×, 60×, 80×, 100×, and 200×, were compared at SNP and Indel detection, and 100× was finally confirmed as the recommend depth. BGISEQ-500 WES performs equally to Illumina at FNR (1.77% to 1.83%) and sensitivity (98.24% vs. 98.17%) of SNP detection, and FNR (10.16% vs. 9.15%) and sensitivity (89.85% vs. 90.85%) of Indel detection. In brief, the WES application on BGISEQ-500 performs equally to that on Illumina platform.

75. OVERCOMING THE ANNOTATION BOTTLENECK — EVALUATION AND VALIDATION OF VARIANT ANNOTATION TOOLS FOR CLINICAL USE

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Genomic technologies are rapidly becoming established in mainstream clinical care with several Australian laboratories routinely performing genomic testing on clinical patient samples. The workflow typically involves multiple processing steps to arrive from raw reads to a set of annotated variants that can be prioritized and reviewed for clinical relevance. While there appears to be a convergence of tools used for read mapping and variant calling, there is a large diversity of approaches taken for the annotation and prioritization of variants. Over the past 3 years, we have developed an in-house tool, VariantGrid, to assist in this task. More recently, a number of commercial software tools have come to market that also address this challenge and these are intended for germline or somatic testing or both, and some offer promising features such as pathway tools, access to curated literature, drug target information, and clinical trial registry. We thus sought to review the functionality of these tools and to design a validation study around the performance of any such tool. Our assessment considered features provided, currency of information, ease of use, software support, flexibility to work with different datasets, cost, architecture (cloud vs. local), type of version control, and ability to integrate with the broader laboratory and reporting workflow. One particular challenge for this project was ongoing updates to these tools. This talk will discuss the findings

and challenges encountered in evaluating and validating variant annotation and prioritization tools for routine clinical use.

76. CLINICAL IMPLEMENTATION OF WHOLE GENOME SEQUENCING FOR THE DETECTION OF POLYCYSTIC KIDNEY DISEASE VARIANTS

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The most common monogenic kidney disorder is autosomal dominant polycystic kidney disease (ADPKD) with a prevalence of at least 1/1,000. ADPKD is an adult-onset disorder resulting in the formation of renal cysts that often leads to end-stage kidney disease and eventually requires costly dialysis or transplantation. ADPKD is caused by disease-causing variants in one of two genes, PKD1 or PKD2. Diagnostic sequencing is currently not part of routine clinical practice due to the confounding presence of six pseudogenes that share 97.7% sequence similarity with exons 1–33 of PKD1. Furthermore, exon 1 of PKD1 and PKD2 are GC-rich and poorly covered by standard PCR-based library preparation. Sequencing of PKD1 can thus not be performed by standard exon capture techniques and traditionally requires laborious and error-prone long-range PCR and Sanger sequencing to overcome pseudogene homology. Using a PCR-free library preparation kit and WGS via the HiSeqX sequencing platform, we have overcome both challenges of sequence homology and GC content. We have validated the Kapa Hyper PCR-free library preparation kit against NA12878 and verified detection of PKD1 and PKD2 variants against 30 previously reported variants detected by LR-PCR. Analytical performance showed 99.87% mapping specificity to PKD1. No false positives were observed in normal controls and clinical sensitivity for detection of previously reported variants was 96–100%. Our clinical implementation of an alternative PCR-free library preparation kit for the detection of ADPKD associated variants now enables access to an accredited diagnostic service for this important condition which has, until now, been difficult to confirm.

77. PARTICIPANT CHOICES TOWARD RECEIVING POTENTIAL INCIDENTAL GENETIC FINDINGS IN AN AUSTRALIAN NEPHROLOGY RESEARCH GENOMICS STUDY

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Background: Potential incidental findings (IFs) in genomics remain a concern for clinicians, scientists, patients, and participants alike. The informed decisions taken by Australian participants with regards to IFs are unclear. **Aim:** To describe Australian participant choices to receiving potential IFs as part of participation

in a nephrology research genomics project. **Methods:** Retrospective review of consent toward IFs was undertaken within a national study of diagnostically refractory inherited kidney disease (05/2014–04/2017). Relative risk, Mann–Whitney *U*-test, and *t*-test analyses were undertaken to assess relationships between audited variables. Results: A total of 133 participants from 33 unrelated families participated. No IFs have been identified to date. A total of 7/133 participants (5.3%) consented to not receive IFs. There were no statistically significant differences between those consenting to receive IFs, or not in terms of gender (male 50.8% vs. 57.1%, $p = .73$), median age (39.42 vs. 45.62 years, $p = .52$), being personally affected by the inherited kidney disease of interest (46% vs. 57%, $p = .53$), consanguinity (18% vs. 0%, $p = .43$), relationship to affected family member/s ($p = .24$ –0.37), or the specialty of the consenting clinician ($p = .19$ –.58). There was, however, a statistically significant difference toward consenting to not receive IFs among those with a family history of another non-renal potentially inheritable disorder (57.1% vs. 8.7%, RR6.55, $p < .0001$) and if the inherited kidney disease of interest had proposed autosomal dominant inheritance (71.4% vs. 30.2%, RR2.37, $p < .0001$). **Conclusion:** The majority of Australian research participants are likely to consent to receive potential IFs. All genetic study participants should be provided with genetic counseling and informed consent prior to participation. Several circumstances may have an impact upon a participant's consenting choices.

78. THE FIRST 271 PEDIATRIC AND ADULT DIAGNOSTIC WHOLE EXOME SEQUENCING REFERRALS: RESULTS AND RECOMMENDATIONS

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Aims: To describe the results of diagnostic WES in childhood and adult Mendelian disorders, analysis methodologies and provide recommendations to maximize the utility of clinical referrals. **Subjects and methods:** Referrals were submitted from clinical geneticists and non-genetic physicians working with genetic counselors. Subjects included families with intellectual disabilities, epilepsy, immunodeficiencies, and a variety of other likely Mendelian disorders. Sequencing libraries were prepared using LifeTech DNA sample preparation kits and robotic instrumentation, and sequenced on an IonProton sequencer with 95% of the exome covered to >20× depth. Raw sequencing reads were aligned to the genome using TMAP with SNVs and indels identified using Torrent Suite. The variants were then filtered with the in-house genomic analysis pipeline including in house and external base frequency data, molecular, and clinical annotations. The genomic data were analyzed by clinical genomicists and reported by genomic pathologists. **Results:** The largest phenotype group, neurological disorders including intellectual disability, and early onset epilepsy, had likely causative pathogenic variants identified in 40%, which were skewed to de novo events. The majority of successful gene diagnoses were based on the analysis of family units (trios) and the involvement of experienced clinicians in the diagnostic process. The overall diagnostic rate was 30.4% with an additional 18% having a possible or novel finding.

79. CLINICAL GENETICS TRAINING IN THE GENOMICS ERA

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Background: Clinical genetic trainees at the Victorian Clinical Genetics Services (VCGS) have recently gained experience in the provision of whole exome sequencing for their patients. The clinical and laboratory services are co-located and there is close collaboration between clinical genetics trainees and laboratory scientists in the provision of whole exome sequencing for patients. **Aims:** We describe the changes to clinical practice since the mainstreaming of whole exome analysis in our service. We also examine the changing education requirements of trainees in light of the evolving role of clinicians in the provision of genomic medicine. **Methods:** The experiences of recently graduated and current trainees over a 3-year period were explored. Interviews were conducted and common themes are identified and described. **Results:** Common themes identified in our interviews are the primacy of phenotyping, interdisciplinary training in variant curation, and interpretation through dedicated laboratory placements and multidisciplinary team meetings, bioinformatics training and genomic counseling training. Additionally, workflow changes have been measured through an audit of inpatient consultations demonstrating that 20% of inpatient consults resulted in whole exome analysis. This growing genomic workload has implications for future job profiles. **Conclusions:** The role of the clinician has changed with the mainstreaming of whole exome sequencing in our service. This has necessitated a broadening of skills required for the provision of genomic medicine. The successful integration of genomic medicine into our work will require fundamental changes to education, training, and workforce planning.

80. DOES GENOMIC TESTING EARLY IN THE CLINICAL TRAJECTORY MAKE A DIFFERENCE? A FOLLOW-UP STUDY

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Background: Genomic testing has transformed rare genetic disease diagnosis, but follow-up studies have not been performed to investigate the longer term impact on patient management, family decision making, and service provision. **Methods and results:** We collected data in a cohort of 80 infants with suspected monogenic disorders who underwent whole exome sequencing (WES). The median duration of follow-up was 473 days (interquartile range 411–650). Uninformative WES results contributed to the diagnosis of non-Mendelian conditions in seven infants. Undiagnosed infants with an ongoing suspicion of Mendelian disorder ($N = 29$) received standard-of-care investigations at a cost of AUD\$15,585 without any additional diagnoses, while WES data reanalysis at a cost of AUD\$11,350 yielded four additional diagnoses. Seventeen patients had changes in management following WES result, with five leading to changes in clinical outcomes. WES diagnosis was not associated with increased tertiary hospital use. The parents of 14 diagnosed children and two undiagnosed children accessed reproductive genetic services at a cost of AUD\$39,517. All couples at

high recurrence risk and achieving a pregnancy utilized either pre-implantation or prenatal genetic diagnosis. One termination of pregnancy occurred in the undiagnosed group, based on uncertainty regarding recurrence risk. Overall, parents of diagnosed children had eight more pregnancies compared to those without a diagnosis. **Conclusions:** These data provide further support for the early use of genomic testing in the diagnostic trajectory, highlighting the value of storage and re-analysis of genomic data, benefits in improved patient management without a major increase in healthcare costs, and restoration of parental reproductive confidence.

81. BUILDING MULTI-LABORATORY CAPABILITY IN EXOME VARIANT CURATION USING LOVD

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Background: The Melbourne Genomics Health Alliance has taken a clinically led approach to delivering genomics to the Victorian healthcare system. Central to this work is implementing technology to enable the application of clinical genomics across multiple diagnostic laboratories, leading tertiary hospitals, and research organizations. A significant challenge in the delivery of routine genomic testing, however, is the labor-intensive process of variant curation that requires a workforce with specialized expertise. **Methods:** The Alliance conducted a 3-year collaborative process across 10 organizations to modify and enhance the popular open source LOVD software and create a shared variant curation tool. The tool was used for Melbourne Genomics Health Alliance clinical flagships, and the experience informed the requirements definition for future implementation of curation systems for Alliance members. **Results:** The development and use of LOVD for variant curation has enabled the Alliance to build workforce capability in genomic variant curation, establish clinically integrated accredited diagnostic workflows and resulted in detailed requirements for future curation software. A consistent approach to variant curation has been achieved across multiple sites and multiple clinical indications. **Conclusion:** The capability and expertise acquired through the in-house development and shared application of LOVD will enable the Alliance to implement long-term solutions to achieve standardized, high quality, efficient variant curation, using the vendor supported Clinical Genomic System for Victoria (GenoVic) that is currently being delivered. The modified LOVD software represents an attractive option for laboratories aiming to establish capability in variant curation, offering a cost-effective, deployable solution.

82. A NOVEL MODEL FOR CLINICAL GENOMICS SERVICE DELIVERY IN AUSTRALASIA

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A Clinical Genomics Unit was established at St. Vincnet's Hospital, Sydney, Australia in 2016, to systematically offer highly

integrated and multidisciplinary whole genome sequencing (WGS) service as a mainstream diagnostic test to adults with rare diseases and/or suspected genetic disorders. Pre-emptive pharmacogenomic testing was also offered to those patients undergoing WGS. This initiative leveraged upon the existence of a world-class WGS facility at the Kinghorn Centre for Clinical Genomics. The aim was to develop a unique clinical-laboratory interface to provide a seamless integration of phenotypic and genomic data to enhance diagnostic rates, and to enable personalized healthcare. Data presented include patient demographics, spectrum of referrals, and clinic structures. Differential models of service delivery pathways for different interdisciplinary clinics were developed. The decision tree, including clinical criteria that determined the types of testing offered (single gene, panel of genes, WGS, pharmacogenomics), patient experiences, and outcomes of testing, will also be presented. Challenges encountered will be discussed, including interconnecting with existing services, demystifying WGS technology (both benefits and limitations), influencing expectations of non-genetics professionals, and helping to shape the evolving role of the clinical genetics professionals in this rapidly advancing era of genomic healthcare. Furthermore, our model challenges the Australian traditional gate-keeper role of a genetics unit. Other important components of our model will be discussed, including training, education, research, technology and infrastructure requirements, benefits of clinical-laboratory interactions, advocacy for state/federal policy on ethical and legal aspects of genomic testing, particularly relating to patient privacy and confidentiality, data ownership, storage, usage, and access.

METABOLIC AND DIET DISEASE MANAGEMENT

83. PROMPT AGALSIDASE ALFA THERAPY INITIATION IS ASSOCIATED WITH IMPROVED OUTCOMES IN THE FABRY OUTCOME SURVEY

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Background: The Fabry Outcome Survey (FOS) collects data from patients with Fabry disease (FD). This post-hoc analysis examined potential benefits of prompt initiation of agalsidase alfa enzyme replacement therapy (ERT) on patient outcomes. **Methods:** FOS patients with FD diagnosis and ERT start dates were included. Renal outcomes included dialysis, transplantation, renal failure, and proteinuria. Cardiovascular outcomes included myocardial infarction, left ventricular hypertrophy, and heart failure. Time to first renal or cardiovascular event from ERT start was compared between prompt (within 24 months of diagnosis) versus delayed (>24 months after diagnosis) ERT initiation. Kaplan–Meier curves were compared with log-rank test. Cox regression analysis with age at time of diagnosis as a covariate was used to estimate hazard ratios (HR) between groups. **Results:** This study included 1,936 patients (934 prompt, 1,002 delayed). Groups were generally comparable by gender, weight, glomerular filtration rate, and left ventricular mass index. Mean ages at ERT initiation were similar, but mean age at time of diagnosis for prompt and delayed groups was 40 and 28 years of age, respectively. Median time between diagnosis and ERT onset for prompt and delayed groups was 7 and 94 months, respectively. Prompt ERT initiation was associated with significant reduction in risk of renal events (HR = 0.779; $p < .01$) and cardiovascular events (HR = 0.768; $p < .001$). **Discussion:** This analysis showed prompt agalsidase alfa initiation (within 24 months after diagnosis of FD) was associated with significantly better renal and cardiovas-

cular outcomes versus delayed initiation (>24 months after diagnosis), suggesting significant benefits with timely initiation of FD therapy.

84. EXPANDING THE DISEASE SPECTRUM OF ECHS1 DEFICIENCY

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Background: Mitochondrial short chain enoyl-CoA hydratase 1 deficiency (ECHS1D, OMIM 616277) is an autosomal recessive inborn error of valine and fatty acid metabolism caused by ECHS1 mutations. The majority of reported patients have presented with a Leigh disease/Leigh-like phenotype, with onset of disease at birth or infancy. Common features include hypotonia, feeding difficulties, developmental delay, regression, lactic acidosis, and characteristic findings on brain imaging. **Case Report:** We report a previously well, developmentally normal 13-month-old boy who presented with severe metabolic acidosis, ketosis, and normal lactate following a brief diarrhoeal illness. He developed jerking movements, left lower limb clonus, and dystonic posturing. Neuroimaging revealed bilateral basal ganglia and brainstem changes, as well as right parietal, occipital, and posterior temporal lobe subcortical and deep white matter changes. **Results:** Whole exome sequencing (WES) was performed under a rapid protocol with time to result of 16 days. WES revealed compound heterozygous ECHS1 variants: NM_004092.3(ECHS1): c.518C>T; p.(Ala173Val) and NM_004092.3(ECHS1):c.541C>T;p.(Arg181Cys). Initial urine screening results when the patient was ketotic were non-diagnostic. Repeat testing when ketosis resolved revealed increased S-(2-carboxypropyl)cysteine-carnitine, typical of ECHS1 deficiency. **Discussion:** The emerging phenotype of ECHS1 deficiency is one of a variable course ranging from neonatal death to survival into adulthood. We highlight the genotype–phenotype correlation of the ECHS1 variant p.(Ala173Val) with later-onset disease and the development of a movement disorder. This case also illustrates that ketosis can be a confounder in the biochemical diagnosis of ECHS1 deficiency, and the clinical utility of rapid WES diagnosis in the acute care setting.

BIOCHEMICAL GENETICS

85. OMEGA-AMIDASE DEFICIENCY: A NEW INBORN ERROR OF GLUTAMINE METABOLISM

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In addition to metabolism to glutamate via glutaminase, glutamine can also be metabolized to 2-ketoglutaric (2KGM) and 2-ketoglutaric in two enzymatic steps catalyzed by glutamine transaminase and omega-amidase, the latter encoded by NIT2. 2KGM is the main omega-amidase substrate and is a reactive molecule that is suggested to be a neurotoxic agent in hyperammonemia. We identified large increases in urine metabolites derived from 2KGM in a consanguineous boy with failure to thrive and lipodystrophy. Omega-amidase enzyme activity was decreased in plasma. His levels of ammonia and plasma amino acids, including glutamine, were normal and there was no clinical evidence of metabolic

decompensations or neurological impairment. Genetic testing identified homozygous mutations in both NIT2 and BSCL2 genes, indicating that he had two coincidental genetic conditions. Mutations in BSCL2 cause congenital generalized lipodystrophy type 2 (CGL2) and the patient's phenotype was consistent with previously described CGL2 patients. Omega-amidase deficiency due to NIT2 mutations has not been previously described and these findings suggest it is a comparatively mild or benign inborn error of metabolism and that 2KGM may not be a significant neurotoxin.

MOLECULAR GENETICS

86. THE MASSARRAY SYSTEM REVEALS SIGNIFICANT POLYMORPHISMS ASSOCIATED WITH ENDURANCE PHENOTYPE AND EXERCISE RESPONSE

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Obesity and exercise intolerance remains a leading social concern and economic burden, often due to cardiovascular disease and other adiposity influenced pathologies. Despite many and varied exercise studies performed to date, the mechanisms behind exercise-induced adaptations remain unknown. In this SNP genotyping project, we utilized the AGENA MassARRAY system to examine 36 previously implicated exercise SNPs for association in the Genomics Research Centre 2008 Hawaiian Ironman Triathlon population (elite athletes). The triathlon participants ($n = 120$) were genotyped and compared to an age/sex/ethnicity matched control population ($n = 77$). Using the PLINK analysis software, four SNPs (rs1799722, rs1799945, rs2294512, rs4994) show significant association with elite athlete status in Caucasian males. We further examined this data through classification of the elite cohort by triathlon finishing time. The cohort was stratified based on finishing time, with the 'top 50%' athletes with a shorter finishing time deemed genetically predisposed to exercise response. In contrast, the remaining athletes (bottom 50%), similar to a moderately trained control population, likely carry polymorphisms associated with a poorer response to exercise training. Following association analysis of the top 50% of the Hawaiian cohort versus the bottom 50% and the control population, significant association was found with the rs1474347SNP within the IL6 gene. In addition to its pro-inflammatory effects, it is one of several such molecules excreted from muscle following acute exercise, indicating the importance of this myokine in acute athleticism. This preliminary data suggests that several polymorphisms may belong to a genetic signature indicative of benefit to exercise training or response.

87. INVESTIGATION OF CARDIOVASCULAR DISEASE SUSCEPTIBILITY MARKERS IN AN AUSTRALIAN HYPERTENSIVE-NORMOTENSIVE POPULATION

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Background: Cardiovascular disease (CVD) is among the leading causes of ill-health and mortality worldwide with >30% of all global deaths directly caused by CVD according to the World Health Organization. It is a multifactorial disease that can be caused by environmental factors as well as genetic factors. Genetic factors include single nucleotide polymorphisms (SNPs), which can be linked with increased susceptibility to CVD risk factors, and potentially epigenetic modifications such as DNA methylation. **Aim:**

To investigate CVD susceptibility markers and identify gender-specific variants associated with blood pressure phenotypes and hypertension in an Australian hypertensive-normotensive population. **Methods:** A genetic replication study was performed on an Australian hypertensive-normotensive population (409 hypertensives and 409 age, sex, and ethnicity-matched normotensive) for candidate markers, to validate findings from a hypertension/blood pressure genome-wide association study (GWAS) carried out in the Norfolk Island (NI) genetic isolate population. The Agena MassArray platform was used to genotype SNPs of interest in the cohort. In addition, we investigated potential epigenetic modifications involved in CVD risk by DNA methylation analysis of candidate genes by pyrosequencing. **Results:** Analysis showed significant association between 11 polymorphisms, initially identified in the NI population with hypertension and blood pressure phenotypes in the case-control cohort, including some gender specific variants. We also found a significant difference in methylation levels of CpG sites at the ATP2B1 gene promoter between the hypertensive and normotensive populations. **Conclusion:** We have identified and replicated novel SNPs, as well as a DNA methylation variant, associated with blood pressure and susceptibility to hypertension.

88. IDENTIFICATION OF NOVEL XQ24-28 FAMILY SPECIFIC CANDIDATE VARIANTS THAT CAUSE COMMON MIGRAINE

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Background: Migraine is a heterogeneous headache disorder affecting a significant proportion of the population with several pathways known to influence its etiology. X chromosome genes and variants have been associated with non-hemiplegic migraine susceptibility; however, no known causative genes or variants have been described to date. With previous association and the predominance of female migraine sufferers, the X chromosome remains a good candidate for further investigation. **Aim:** To identify causal novel variants in the Xq24-28 chromosomal region. **Methodology:** We employed paired-end Next Generation Sequencing (NGS) of the ~37Mb Xq24-28 chromosomal region on 24 DNA samples from 6 X-linked migraine family pedigrees available within the Genomics Research Centre. Identified variants were annotated and filtered to include those of the highest quality, along with missense, non-sense, frameshift, or in-frame annotation in affected individuals and absent in non-affected individuals in each family. Variants were visualized using the integrative genomics viewer for subsequent validation by Sanger sequencing. **Results:** We identified 18 variants in 7 genes as potential migraine candidates and we are currently validating these in the migraine families. These variants will then be examined in additional population cohorts to determine their association with migraine. **Conclusions:** The identification of rare functional genetic variants associated with common migraine and familial migraine, will provide a better understanding of the functional consequences of these variants and establish new candidate genes for future migraine research and the development of improved diagnostics tools.

89. AUSTRALIAN RENAL GENE PANELS: RESULTS FROM A NATIONAL DIAGNOSTIC SERVICE

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Inherited renal diseases are genetically heterogeneous with both multiple genes contributing to specific phenotypes and single gene defects having multiple clinical presentations. Massively parallel sequencing (MPS) allows testing for disorders involving many genes. A multidisciplinary group of nephrologists, clinical, and molecular geneticists have developed 17 Renal Gene Panels according to reported association with renal phenotypes, including Alport syndrome, complement dysregulopathy, nephrotic syndrome, and autosomal dominant tubulointerstitial disease. Referrals were accepted from August 2014 and include more than 250 probands. MPS was performed using the Illumina TruSight One panel capture on an Illumina HiSeq 2500 or NextSeq 550 and variants were analyzed for the genes in the required panel. Preliminary results show 43% of patients had an identifiable disease-causing variant. Where clinical phenotype is clearly defined, the diagnostic rate was high in both adult and pediatric cohorts (Alport's 80% and 88%, respectively; tubular 75% both). However, where a condition displays heterogeneous genetic etiology, detection rate was generally higher in the pediatric compared to the adult cohort (complement mediated disease 64% vs. 17% and ciliopathies 47% vs. 29%). We have successfully implemented genetic testing for renal diseases with the diagnostic yield varying according to age at presentation and renal phenotype. Mutation detection rates can provide information of the likelihood of identifying a disease causing variant for each panel prior to testing. Furthermore, an accurate genetic diagnosis helps inform clinical management, guides prognosis, reduces the need for invasive investigations, may identify specific treatments, and aids in genetic counseling and family planning.

90. THE GENETIC SPECTRUM OF HEMIPLEGIC MIGRAINE ASSESSED USING A TARGETED NEXT GENERATION SEQUENCING MULTI-GENE PANEL

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Background: Hemiplegic migraine (HM) is a rare subtype of migraine with aura characterized by severe attacks of typical migraine accompanied by hemiparesis, as well as episodes of complex aura that can vary significantly from confusion through to coma and may be fatal after minor head injury in rare cases. HM has been found to be caused by mutations in the CACNA1A, ATP1A2, and SCN1A genes. **Method:** We have recently developed a comprehensive and highly efficient strategy for complete molecular diagnosis of the three known HM genes, as well as genes that cause related conditions (NOTCH3 and KCKN18), based on multiplexed targeted resequencing of the five genes using next generation sequencing (NGS). In this study, we have sequenced genomic DNA from 172 HM sufferers, for whom we had not previously found mutations by Sanger sequencing (SS) of selected exons in HM genes, using

the NGS panel. **Results:** Mutational screening of 172 suspected HM cases resulted in identifying 29 potentially causative mutations in 35 cases (20.3%) using the NGS approach in four genes (CACNA1A, ATP1A2, SCN1A, and NOTCH3). All detected mutations were confirmed by SS and were absent in 100 non-migraine healthy unrelated control individuals. **Conclusion:** Our targeted NGS gene panel has increased the diagnostic yield by four fold over the previously used method of iterative SS. Our results suggest that prioritizing use of NGS multi-gene panels to screen ATP1A2 alongside CACNA1A and SCN1A is clinically useful and efficient method to identify mutations causing HM in the Australian population.

91. LOW-LEVEL GERMLINE MOSAICISM BY NGS: CLINICAL SIGNIFICANCE AND UPDATE OF CURRENT TESTING AT SA PATHOLOGY

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Next-generation sequencing (NGS) allows detection of genetic variants in cell subpopulations in varying tissue types to confirm low-level mosaicism that may have otherwise been missed by preceding technology. With consideration that low-level mosaicism may affect surveillance and familial predictive testing, SA Pathology is currently evaluating an NGS platform for tumor sample testing for pathogenic variants associated with inherited cancers with respect to determining low-level germline mosaicism. A custom-designed Roche panel of 1,000 genes of interest was selected as the platform to use. Some challenges to this testing are tissue integrity such as the heterogeneity of the sample and preservation of tumor and technical challenges such as sequencing depth, sensitivity, and varying tissue types out-competing others. The variants identified and the allelic fraction detected give rise to challenges in interpretation and reporting. Inheritance risk cannot be excluded when low-level mosaicism is detected but its absence and hence somatic origin can exclude the need for familial predictive testing or frequent surveillance. Germline and somatic mosaicism has been under-represented in all cancers and diseases, and now with deep sequencing technologies, the future direction for variant detection and germline mosaicism testing on NGS platform at SA Pathology is collating data to define parameters for sensitivity levels with high confidence. This presentation describes how the clinical relevance of detection of low-level mosaic variants will benefit the patient and their families by way of counseling and monitoring.

92. OUTCOMES OF CYSTIC FIBROSIS CARRIER SCREENING IN VICTORIA

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The Victorian Clinical Genetics Services (VCGS) provide genetic screening for cystic fibrosis (CF) to determine an individual's carrier status in the general population either as a single test or as part of the reproductive genetic carrier screening program. CF is a highly variable disorder where clinical manifestations range from mild to very severe. Approximately 2,000 gene sequence variants have been identified in the CFTR gene. Testing in our screening program involves testing for 38 variants in the CFTR gene, which account for ~90% of CF carriers in the Australian Caucasian population. Inclusion of variants in the panel was based on recommendations

by the American College of Medical Genetics (ACMG), their frequency in our population and the severity of the variants. Testing of the CFTR 38 panel is performed using the MALDI-TOF mass spectrometry assay. Screening of 12,000 individuals from the reproductive screening program has provided a useful insight into the local population with 1 in 35 individuals identified as carrier of CF and the frequencies of the CFTR variants with 79.8% of CF carriers having p.F508del followed by p.G551D at 3.8%, p.G542* at 2.9%, p.N1303K at 2.6%, and p.W1282* at 2.4%. Ethnic variation was highlighted in our program with some individuals identified as carriers of severe CFTR variants not in the ACMG list of recommended CFTR variants. Further analysis of CFTR variants in our clinical cohort is underway to ensure we provide a relevant and comprehensive screening panel with the ethnic diversity of the local population in mind.

93. SALIVARY GLANCE – A BRIEF REVIEW OF VALIDATION OF SALIVA AS A SPECIMEN TYPE

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Introduction: Saliva and buccal swab samples are swiftly becoming the favored method of DNA collection by clinicians due to their ease of collection and avoidance of an invasive procedure. The SEALS Genetics laboratory has validated saliva as a specimen type for extraction of DNA using the GeneFIX Isohelix Saliva Collector kit and QIASymphony DNA extractor. Specimen validation included a total of 81 specimens from consenting individuals, consisting of 72 healthy volunteers, and 9 individuals previously confirmed to be either CF carriers or CF-affected individuals. **Methods:** Sixty-four specimens were collected following the manufacturer's collection protocol. The remainder were collected for specific validation components; to determine the effect of the volume of saliva collected in the tube, consumption of food and drink prior to collection, and the stability of the stored specimens over time. The validation involved extracting DNA and subsequently measuring the quantity and quality using a spectrophotometer followed by running the extracted DNA through several assays in the laboratory to assess suitability and performance. **Results:** It was found that based on DNA quality, quantity, and performance on assays, the consumption of food and drink, in the 30 minutes prior to specimen collection has a negative effect on the DNA extracted. The DNA yield of a specimen was also found to be proportional to volume of saliva collected. **Discussion:** Despite the effects of volume and of food and drink consumption, all specimens excluding two were of sufficient quality for testing.

94. DUCHENNE MUSCULAR DYSTROPHY FAMILY TESTING – HOW FAR WOULD YOU GO?

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Duchenne and Becker muscular dystrophy (DMD/BMD) are caused by mutations within the dystrophin gene. Family testing using MLPA or Sanger sequencing detects deletions and duplications, point mutations, and small insertions within the gene. We were presented with two different case studies with little or no information on the familial mutation. The first case involved a proband tested in India through a diagnostic testing service under research conditions whereby a single exon deletion was reported. A pregnant relative had requested carrier testing for possible future prenatal diagnosis. No sample from the proband was available. Our MLPA test did not detect any deletions, while Sanger sequencing of that region was performed to exclude SNPs that may have influenced results. The results did not exclude the possibility of a false positive in the proband or point mutations that may not have been detected. The second case

was a mother with two deceased sons affected with DMD requesting carrier testing. With no information on the familial mutation, MLPA analysis and whole gene sequencing by Next Generation Sequencing was requested. MLPA testing detected a two-exon deletion. An additional test was developed to confirm this deletion in a 40-year-old Guthrie sample from one of the sons. Different standards of testing internationally highlight the complexity involved with detecting familial mutations and variations in test methods. These cases emphasize the challenges in validating a familial mutation without available proband sample or mutation information, as well as consideration of cost and time invested.

95. CURATION OF THE AUSTRALIAN RENAL GENE PANELS

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Massively parallel sequencing (MPS) has opened up the possibility of testing numerous genes associated with a particular phenotype. This was first performed using custom panels of genes previously tested by Sanger sequencing. However, now virtual panels of genes are created from clinical exomes, whole exomes, or whole genomes. The technical advance shifted an emphasis toward inclusivity of all genes with a possible association to a particular phenotype. However, this resulted in the identification of a high number of variants of uncertain significance in genes with only limited evidence for involvement, which increased the difficulty of reporting and interpreting. To date, panel curation has been performed by clinical and research experts using their professional skills. More recently, the ClinGen initiative (<https://www.clinicalgenome.org/about/>) has developed an objective approach of evidence weighting similar to the ACMG guidelines for variant curation. Evidence classifications have been divided into definitive, strong, moderate, limited, no reported evidence, and conflicting evidence categories. In 2014, the Australian Renal Gene Panels (ARGP) was introduced as a clinical diagnostic service; 17 specific panels are offered and over 250 proband referrals have been received. Panels were originally curated by a working group (authors above) consisting of nephrologists (adult and pediatric), clinical geneticists, and molecular geneticists. The ClinGen scoring system will now be applied to these panels to facilitate further curation. The use of the ClinGen gene curation system will allow for better reporting standards and for easier updating of genes as evidence levels change.

96. FUTURE PROOFING GOOD LABORATORY PRACTICE. HOW TO AVOID THE HIDDEN SNP AND A MISDIAGNOSIS

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Participation in quality assurance (QA) programs is a critical process for all diagnostic laboratories. Not only is this a NATA requirement, but it is essential that we continue to maintain updated, current work practices to ensure we are providing the correct patient result. Reporting practices are scrutinized, and improvements proposed to ensure laboratories are clear and adhere to both current

HGSV nomenclature and appropriate gene transcript. Methods used for molecular testing are also scrutinized. Through participation in QA programs, laboratories are able to tap into this knowledge base and the experience of others; be it the limitations of certain assays, older methods may become redundant as new, alternative technologies emerge, or simply access to new gene information. One ingredient critical to our work is primers as PCR amplification is the first step in many assays. Our laboratory recently participated a Mitochondrial UK-NEQAS program and misreported a POLG variant as homozygous, when in fact the variant was heterozygous. There was a SNP underneath one primer, just recently identified and published. To distinguish between true homozygous and allele drop-out, segregation testing of parents is critical. However, we also need to ask: Do primers have an expiry date? With expanding population data sets, new SNP builds, should all primer designs be reviewed annually? As we embark on the future with new technologies and an increasing number of new laboratories performing diagnostic tests, what can we do to future proof good laboratory practice? What standards and guidelines must laboratories incorporate to prevent erroneous results?

97. A WHOLE GENOME SEQUENCING APPROACH TO CVD GENE DISCOVERY

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Cardiovascular disease (CVD) is the leading cause of mortality worldwide and encompasses conditions of the heart and vasculature. CVD risk is attributable to several factors including blood pressure, smoking, increasing age, sex, and genetics. Although CVD risk is heritable and there have been a number of successes localizing QTLs that influence disease risk, the genetic basis is still relatively unknown. Here we show the utility of WGS for the discovery of CVD risk genes. Initially, we searched for variants influencing CVD risk by focusing on rare NS mutations. We identified multiple rare variants (minor allele frequencies < 0.005) significantly associated with CVD in our large pedigrees including a pair of variants in compete linkage disequilibrium on chromosome 1 in the PIGC and RABGAP1L genes whose heterozygotes exhibit more than four times the risk for disease as their common homozygotes. Similarly, a rare deleterious NS variant in the LSS gene is associated with a nearly three-fold increase in CVD risk. In a complementary approach, we looked for evidence of association in a genomic region previously implicated in phospholipid levels. We identified an unequivocal genome-wide association between a SNP (rs174556; MAF = 0.40) in the FADS1 fatty acid desaturase gene that was associated with large increases (0.4 to 0.75 SDU) in phosphatidylcholines ($p = 7.5 \times 10^{-66}$), lysophosphatidylcholines ($p = 4.1 \times 10^{-48}$), cholesterol esters ($p = 1.0 \times 10^{-26}$) and diacylglycerols ($p = 8.1 \times 10^{-19}$). This variant resides in a known transcription factor binding region of FADS1. These associations represent strikingly large biological effect sizes for such a common variant.

98. VARIANT DETECTION AND MASSIVELY PARALLEL SEQUENCING: I'VE GOT SOME GOOD NEWS AND SOME BAD NEWS!

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Background: The introduction of Massively Parallel Sequencing (MPS) has significantly increased the number of genes that can be

sequenced at the one time, enabling a broader search for clinically significant variants. However, a main concern is whether this change decreases the overall sensitivity of the testing. **Aim:** To assess the efficacy of variant detection using MPS, highlighting both the limitations and benefits as compared with Sanger sequencing. **Methods:** Known positive samples were examined by MPS using Illumina-based systems. An internal control sample was used to investigate assay reproducibility and the capacity of MPS to detect copy number variation was assessed. **Results:** Analysis of known variants and the control sample has shown that, for the vast majority of variants (>99%), MPS is very reliable at variant detection and calling. However, a number of specific types of variants were more likely to be either missed or mis-called using MPS. Detailed analysis showed that these were caused by issues with the sequencing chemistry, read alignment, and/or variant calling. In contrast, by the comparison of relative read depths, MPS has been successful in detecting multi-exon and single exon deletions and duplications. **Conclusion:** Although MPS is highly reliable at detecting the majority of variants, it does lead to a slight decrease in sensitivity as compared with Sanger sequencing. However, it does have the added capacity of being able to detect copy number variants.

99. HUMAN AND MOUSE FGF9 MISSENSE MUTATIONS RESULTING IN XY GONADAL DYSGENESIS

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Patient screening of 29 46 XY GD patients with a 1,032-gene DSD sequencing panel identified the missense variant in FGF9, D195N and in silico analysis predicted the D195N variant to be deleterious for FGF9 protein function. The D195 residue lies at the homodimerisation interface. Wildtype and mutant FGF9 were produced in *E. coli* and purified. FGF homodimerization is facilitated by heparin; however, FGF9-D195N protein shows reduced binding to its co-receptor, heparin, and a reduced proliferative response in a gonadal cell line. In addition, a mouse FGF9 'knockin' mutation FGF9-N143T with highly similar biochemical deficiencies to D195N (in heparin binding and homodimerisation) shows partial XY gonadal sex reversal with a truncated coelomic blood vessel and partial sex reversal. Essential for testis development is the known role of FGF9 signaling to repress the pro-ovarian RSPO1-WNT4 pathway. Recently using a FGFR2c^{-/-};Foxl2^{-/-} knockout mouse, we have identified that testis development also relies on FGF9 signaling to repress the separate, but complementary, FOXL2 pro-ovarian pathway. Notably, XY Fgf9N143T/N143T gonads show ectopic activation of FOXL2 expression but not WNT4 expression. Therefore, a key role of FGF9 signaling for testis development is the repression of the expression of the ovarian factor FOXL2. Together, these results suggest that FGF9 homodimerization and heparin binding are required for FGF9 anti-ovarian function in testes determination. In addition, human FGF9 mutations may be the cause of a subset of hitherto undiagnosed human DSD patients.

100. PRECONCEPTION SCREENING USING ILLUMINA INHERITED DISEASES PANEL

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Preconception screening was originally offered to specific ethnic groups, most notably those of Ashkenazi Jewish ancestry, due to the high carrier rates for a number of specific genetic syndromes.

With the advent of NextGen Sequencing (NGS), it is now possible to screen individuals for carrier state for a larger number of genes at an acceptable cost. With access to the internet, more patients are searching for screening tests available prior to starting a family. The first commercial and widely was that offer as the Counsyl test covering 108 genes and 417 mutations. NGS allows all coding regions of a gene to be sequenced allowing detection of a much greater number of mutations in any one gene. Such screening is now allowing a more complete assessment of mutation carrier frequencies rather than relying on determination from the number of affected individuals in the population. We chose to introduce the Illumina Inherited diseases panel as a preconception screen as it focuses on autosomal recessive conditions affecting children and does not contain cancer predisposition or adult onset diseases. Utilization of the panel is by couples planning pregnancy and IVF gamete donors. Currently we have screened 161 individuals. Between 2,800 and 3,000 variants have been identified by sequencing per patient, yielding 280–350 variants for tertiary analysis. Two hundred and fifty pathogenic variants have been reported. One individual had five pathogenic variants and 37 had none. The three most common disorders with pathogenic variants were CFTR (7.5%), MEV5 (5%), and SLC37A4 (5%).

101. REPRODUCTIVE GENETIC CARRIER SCREENING: CONSIDERATIONS FOR INCLUDING SPINAL MUSCULAR ATROPHY

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Since 2012, Victorian Clinical Genetics Services has been offering a novel integrated genetic carrier screen for cystic fibrosis, spinal muscular atrophy (SMA), and fragile X syndrome in pre- or early pregnancy through general practice, obstetrics, fertility, and genetics settings. Genetic counseling and pre-natal/pre-implantation diagnosis is available to those at increased risk of having a child with these conditions. Although SMA carrier screening meets many screening criteria due to its severity, high carrier frequency, and accurate carrier test, the genetics of SMA are complex posing challenges for population screening. To date, more than 16,000 individuals have undertaken screening, identifying 1 in 20 individuals to be carriers of one or more conditions, most with no family history. Of those, 323 (2%) were carriers of SMA, with testing in over 95% of carriers' partners identifying two carrier couples. Both carrier couples underwent prenatal diagnosis (one affected fetus). Our experience has provided valuable insight into the frequency of SMN1 alleles in our population. Challenges of population screening included explaining the complex genetics and varying clinical severities of SMA to carriers with no prior knowledge of SMA, prenatal diagnosis for carrier couples including requests for non-standard SMN2 copy number testing, and the recent introduction of clinical trials for SMA. The availability of genetic counseling support and a collaborative approach between laboratory teams, genetics services, specialist pediatricians, and support organizations was essential in managing these challenges appropriately and effectively delivering a carrier screening service for SMA.

102. TRANSCRIPTOME ANALYSIS OF HUMAN STEM CELLS IDENTIFYING PROTEOGLYCAN AS POTENTIAL BIOMARKERS OF NEURAL LINEAGE SPECIFICATION

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Human mesenchymal stem cells (hMSCs) self-renew and possess multi-lineage differentiation potential, including the neural lineages (neurons, astrocytes, and oligodendrocytes). Cell lineage differentiation potential is often influenced by the localized microenvironment or niche, in which the extracellular matrix (ECM) constituent proteoglycan (PG), is a major component. Recent findings by our group have identified specific heparan sulfate PG core proteins, syndecans, and glypicans, as potential novel markers of neural lineage specification by demonstrating their role in hMSC and human neural stem cell (hNSC) maintenance and neural lineage commitment. hMSC populations ($n = 3$) were differentiated under neural lineage culture conditions through direct terminal differentiation and terminal differentiation via hMSC-induced neurosphere formation. RNA and protein were collected throughout differentiation at days 7, 14, 28, and 40 during basal lineage differentiation conditions. Gene expression analysis by Q-PCR identified several significant gene expression changes in PGs between neural specific culture conditions and stages of differentiation. This data suggests PGs, in particular members of the syndecan and glypican families, may be key players in hMSC neurogenesis. Further characterization by transcriptome profiling and pathway analysis of hMSC neural cultures is in progress to identify the PG-mediated pathways regulating neural lineage specification. A deeper understanding of the complex and dynamic processes mediating human neurogenesis will provide important information to these central cellular process, as well as enable advances in stem cell therapy for application to the understanding and repair of neurological disorders.

103. REARRANGING WORKFLOW TO IMPROVE TURN-AROUND TIME FOR GENETIC TESTING: DOING MORE WITH LESS

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Introduction: Demand for genetic testing continues to rise. In an environment of cost containment, the four physically separate laboratories that offer molecular genetic testing in our service continue to see an increase in test requests of between 15% to 20% per year, with little or no capacity to increase staffing. In the contemporary model, all requests for cascade testing of at-risk family members, as well as variant confirmation and family segregation studies following next generation sequencing have been performed by the 'parent' laboratory responsible for the original test, with turnaround times of up to 16 weeks. **Method:** All requests for cascade testing, variant confirmation, and family segregation were internally centralized to a single laboratory that had access to robotic equipment. A standardized modular work flow was developed to replace the 'specific case' model. **Results:** In the first month of centralization, 145 Sanger sequencing tests were performed. Turnaround times for this new service were reduced to a median of 14 days (range 4–33). In the subsequent 3 months, further development of procedures reduced turnaround times to a median of 8 days (range 3–17). **Conclusion:** Designing new workflows to work smarter, rather than harder, has resulted in improved turnaround times despite an increased number of test requests. We continue to look at ways to streamline testing despite a geographically dispersed physical laboratory structure.

NEUROGENETICS

104. IDENTIFYING THE GENETIC CAUSE OF FAMILIAL PARKINSON'S DISEASE IN A HIGHLY TRIAGED COHORT OF PATIENTS

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Parkinson's disease is the second most common neurodegenerative disorder, affecting 1 in 350 Australians, with more than 30 new diagnoses each day and 6.3 million people affected worldwide. Approximately 15% of patients report a family history, indicative of a heritable genetic defect, this often leads to a younger age of onset than the sporadic form of the disease. Clinically, Parkinson's disease has significant overlap with many other movement disorders, including dystonia, frontotemporal dementia, motor neuron disease, and paroxysmal dyskinesia, making diagnosis challenging. Identification of a genetic cause for heritable Parkinson's disease may provide unaffected family members with the opportunity for presymptomatic or prenatal testing, and the possibility of individualized therapy. A cohort of 20 patients with familial Parkinson's disease was selected by a movement disorder expert. A panel of 70 genes causatively implicated in movement disorders was interrogated using Next Generation Sequencing. Single nucleotide changes, small insertions and deletions and CNVs were assessed and classified using ACMG guidelines. Potential disease causing variants were identified in 18/20 of the familial Parkinson's disease patients. The majority of variants identified were novel, with insufficient data to definitively classify the variants. A targeted movement disorder panel applied to a well triaged cohort of patients was highly effective at identifying potential disease causing variants. However, without a definitive mechanism of pathogenicity or strong supporting functional data, the clinical benefit to family members remains limited. As our capacity to identify genetic variants increases, so to must our proficiency in interpreting the clinical implications of these changes.

105. POTENTIAL ROLE FOR CADM2 SNP IN VISUAL MEMORY, PROSPECTIVE MEMORY, AND EXECUTIVE FUNCTION IN HEALTHY INDIVIDUALS

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Background: The common polymorphism rs17518584 near the cell adhesion molecule 2 gene (CADM2) was previously identified as playing a role in processing speed and executive function in a genome-wide association study performed in a cohort of non-demented older adults. In this study, we investigated this polymorphism in a younger, healthy population cohort, with no reported incidence of memory or psychiatric disorder. **Research question:** We examined the rs17518584 polymorphism in a cohort of healthy younger individuals for association with cognitive function and memory. **Methods:** We phenotyped 619 individuals for memory and executive function using a battery of tests that measured visuospatial memory, working memory, prospective memory, retrospective memory, verbal memory, and frontal lobe functions (visual scanning, graphomotor speed, and cognitive flexibility). Genotyping of rs17518584 was undertaken by RFLP (restriction fragment length polymorphism) analysis. Analysis was performed using multiple regression analysis while controlling for demographics to test for association of the polymorphism with the proposed phenotypes.

Results: The CADM2 polymorphism was found to be significantly associated with processing speed ($p < .05$, $B = -3.19$, $t = -2.19$) and prospective memory ($p < .05$, $B = 0.16$, $t = 2.36$). No significant association was found with visual or retrospective, or working memory, as well as cognitive flexibility. **Conclusion:** The findings of this study support a role of CADM2 in aspects of human memory and executive function. Further investigation is needed to explore the specific pathways of this role.

106. MICRORNAS AS BIOMARKERS FOR ALZHEIMER'S DISEASE – VALIDATION IN AUSTRALIAN AND CHINESE POPULATIONS

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Background: Recently, microRNAs (miRNA) have been identified as a potential biomarker for Alzheimer's disease (AD). To maximize clinical utility, however, miRNA biomarkers should be applicable across different ethnic populations. **Aim:** We aim to identify common miRNAs differentially expressed in peripheral blood of well-phenotyped Australian and Chinese patients with AD and normal cognition. **Method:** Cross-sectional miRNA expression was investigated using blood RNA collected from 48 Australian Caucasian participants with established clinical diagnoses (16 AD, 16 mild cognitive impairment [MCI], and 16 normal cognition) using the Agilent microarray. MiRNA data were normalized and expression compared across the diagnostic groups. Similarly, miRNA expression analyses were performed for an age- and gender-matched Chinese cohort. Significant miRNAs in both the Chinese and Australian cohorts were selected for validation. **Results:** Many miRNAs ($n = 126$) were significantly differentially expressed between patients with AD and normal cognition in the Australian cohort, and 45 miRNAs were differentially expressed in the Chinese cohort. MiR-550a-3p was significantly upregulated in AD compared to controls in both the Australian ($p < .05$) and Chinese groups ($p < .05$), and similarly upregulated in AD compared to MCI. There were no significant differences between MCI and control groups. **Conclusion:** Peripheral blood miRNAs have potential to be biomarkers for AD. MiR-550a-3p has not been previously investigated. It was identified in both the Australian and Chinese cohorts and may be useful as a biomarker candidate for AD across different ethnic populations. Further studies are needed to replicate and extend these results in independent cohorts from other ethnic backgrounds.

107. WITHDRAWN

108. SEQUENCE ANALYSIS OF MECP2 AND CTNND2 GENES IN HELLER'S SYNDROME SUSPECT CASE

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Childhood disintegrative disorder (CDD), or Heller's syndrome, along with Rett's syndrome are part of severe autistic spectrum disorder (ASD) with similar symptoms and are examples of abnormality in postnatal growth and development of neurons. Many reported Rett's syndrome cases are linked with MECP2 mutation, and the

latest study has shown a new link to mutation of CTNND2 gene in some ASD cases. In this study, proband is a suspect individual with phenotypes of severe ASD. The objectives of the study are to align genomic DNA sequences (exon 2,3,4 of MECP2 and exon 3,5,7,8 of CTNND2) of proband, her mother, and her two siblings to eventually find the proband's causative pathogenic mutation and its inheritance pattern. The acquired genes' sequence are aligned and analyzed with Sequencher software. The result of this study successfully found a pathogenic de novo mutation in exon 4 MECP2 gene of proband. The mutation changes the cytosine of CGA codon into thymine (CGA to TGA) at coding sequence position 880 and caused early termination (p.Arg294Term) of methyl-CpG-binding protein 2 (MeCP2) protein synthesis which implicate to the lost of 192 amino acids at the C-terminal from the total of 486 amino acids in functional MeCP2. The MeCP2 transcriptional regulator function of neuronal genes is impaired by this mutation, especially on the crucial process of synaptogenesis and cell maturation, which induces the abnormal growth and development of normal brain function in proband. Meanwhile, the sequences of CTNND2 gene analyzed in this study are all identical.

109. ISSUES OF CONSENT IN GENETIC TESTING FOR DEMENTIA: FOUR CASE EXAMPLES

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Background: Genetic testing for dementia raises issues relating to informed consent. Genetic counseling approaches to consent are based on the ethical principles of autonomy, beneficence, and non-maleficence. Traditionally, this requires the client to gain enough understanding of the genetic condition(s) so that they can appraise the benefits and harms of the result for themselves and their family. This becomes more challenging when the client's cognition and capacity for empathy becomes progressively impaired. **Case Discussions:** Here we present several case examples, where ethical and practical issues relating to consent occurred. Case 1: A woman in her 40s affected by frontotemporal dementia (FTD), with no assigned medical power of attorney (POA). Complex family dynamics existed, raising issues of non-disclosure. Case 2: Genetic testing for Alzheimer's disease (AD) in a 45-year-old woman with four teenage children; her mother consented as proxy, causing distress for the proband's sisters. Case 3: Panel testing for a woman diagnosed with early onset AD where she did not bring a relative or support person to the genetics appointments. Case 4: A 38-year-old non-English speaking man with FTD whose POA, the Office of the Public Advocate, consented to genetic testing without involving the family. **Conclusions:** Genetic health professionals often face ethically complex situations in relation to consent to dementia genetic testing. These cases clearly demonstrate that a flexible approach is necessary, and ethical approaches must consider the impact and the attitudes of genetic testing for multiple family members.

110. FAMILY SEGREGATION ANALYSIS IDENTIFIES A NOVEL GENE POSSIBLY ASSOCIATED WITH FAMILIAL HEMIPLEGIC MIGRAINE

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Background: Familial hemiplegic migraine (FHM) is an autosomal dominant neurological condition. FHM symptomatology is varied and commonly overlaps with similar neurological disorders (CADASIL & EA2) — making it difficult to diagnose (diagnostic success <23%). Due to these diagnostic limitations, FHM management and treatment is sub-par and the understanding behind the pathophysiological consequences of geno-phenotype associations are constrained. **Aim:** We aimed to identify new FHM causative

mutations and translate these findings into an improved next-generation sequencing diagnostic test. **Methods:** Whole Exome Sequencing (WES) was performed on a family comprised of three affected FHM members and two unaffected members. WES data were analyzed using a bioinformatic pipeline that works through a number of filtration and variant prioritization steps. First-pass analysis removed common/hotspot variants and functionally insignificant variants based on a minor allele frequency (MAF >1% [1,000G, ExAC, gnomAD]) and in-silico predictive functionality scores (SIFT >0.05; Polyphen <0.80). Second-pass analysis removed non-disease specific variants based on comparisons with unrelated controls ($n = 5$) and benign variants reported in ClinVar/LOVD/HGMD. Third-pass analysis classed variants based on gene ontology into five groups. Short-listed variants were assessed based on IGV observation and read coverage. Remaining variants were validated with Sanger Sequencing. **Findings:** To date, our results have identified three novel mutations segregating with affected family members in a single gene. **Conclusion:** This ongoing research will enable a more complete understanding of the biological and genetic basis of FHM. Advances in FHM diagnostics will lead to improved patient outcomes by substantially increasing the rate of diagnostic success.

111. GENOME-WIDE ASSOCIATION STUDY OF COGNITIVE TRAITS: INTELLIGENCE, LEARNING, AND MEMORY

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The complex and highly polygenic traits of intelligence, learning, and memory are fundamental functions of neurocognition. Despite evidence from several genetic and twin studies implicating several genes and attributing heritability, neurocognition functions are highly variable between individuals and remain poorly understood. The investigation of intelligence, learning, and memory using a large, well-defined, and healthy cohort in a genome-wide association approach was utilized to examine the contribution of genetic variance to neurocognitive performance variability. The Genomics Research Centre memory cohort consists of 619 individuals, of whom two-thirds are female and ranging in age from 16 to 68 years (with a median age of 20 years). Phenotypic data was collected from the cohort encompassing eight comprehensive tests (comprised of 21 cognitive performance assessments), including the evaluation of full-scale IQ along with five learning measures for visual and verbal learning, and 15 different memory measures for major types of memory (semantic, episodic, and prospective memory). Statistical analysis was completed using a generalized linear model with covariates age, gender, and population structure. Initial analysis was performed for each phenotype independently, followed by a phenome approach. Preliminary analysis indicates polymorphisms in several genes with associations (p value < 10⁻⁵) to intelligence, learning, and memory performance, with few of them successfully replicated in a similarly characterized cohort. The investigation of genetic associations with a wide variety of neurocognitive phenotypes in healthy individuals may provide an increased understanding of the genetic contribution to human cognition and may have important consequences on managing disorders with cognitive impairments.

112. INTEGRATED OMICS DISCOVERING CLINICALLY RELEVANT COPY NUMBER AND SEQUENCE VARIANTS IN CEREBRAL PALSY

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Cerebral palsy (CP) describes a group of heterogeneous disorders affecting movement and posture that are caused by a non-progressive lesion or abnormality in the pre or postnatal brain. Comorbidity of CP and disorders with predominantly genetic origin such as intellectual disability and epilepsy suggests that a similar genetic contribution to CP is likely. Our initial exome study of 98 trios yielded a conservative molecular diagnostic rate of 14%; however, a further 44% had variants of unknown significance. In this study, interrogation of existing exome data from 198 probands, in combination with RNA-Seq from 182 patient derived lymphoblastoid cell lines (LCL), yielded an improved interpretation of variants of unknown significance and facilitated discovery of copy number variants. We discovered six deletions and eight duplications in the exome data that were validated by Illumina Infinium CytoSNP-850 arrays. Expression of consecutive genes in each CNV was altered consistent with gene dosage. Outlier expression levels detected in other samples provided validation of premature termination or splice site defects in a further nine genes. Integrated 'omics' analysis of our exome, RNA Seq, and SNP array data brings our current likely pathogenic variant rate to 25% for this cohort supporting a significant contribution of genetics to CP. Differentially expressed genes in the whole cohort were enriched for trophic signaling pathways. Weighted gene coexpression analysis also revealed the genetic landscape of CP shares significant overlap with genes implicated in autism spectrum disorders suggesting a possible link between these two neurodevelopmental disorders with known environmental and genetic components.

113. UNCOVERING THE MISSING GENETIC COMPONENT OF FAMILIAL MOTOR NEURON DISEASE

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Motor neuron disease (MND) is an ultimately fatal, genetically heterogeneous neurodegenerative disease. Approximately 10% is hereditary (familial). While gene mutations are the only proven cause, one-third of MND families carry an unidentified mutation. These families are often small and exhibit incomplete penetrance, inhibiting traditional disease gene mapping. Using next generation sequencing and custom bioinformatics, we applied innovative approaches to identify novel genetic contributors to familial MND. Analysis of four MND families identified 52, 55, 66, and 112 shared variants, respectively. Custom filtering reduced these numbers to 21, 24, 22, and 74. Having exhausted gene mapping in these families, the potential pathogenicity of each variant was assessed in silico, using protein predictions, conservation, genic tolerance, and presence in other MND cohorts. By ranking genes most likely to cause MND, just a handful of high priority variants were selected for downstream in vitro analysis. A fifth family underwent linkage analysis, and has been sent for whole genome sequencing. Shared variant analysis and exclusion of loci with evidence against linkage has potential to identify a novel MND mutation in this family. Additionally, 36 candidate genes implicated in disease by proteomic, transgenic models, or other genetic studies were screened through 61 probands. Five novel variants were identified and processed through the above ranking

pipeline. Further, 14 known variants were found to be either over- or under-represented in MND patients. Elucidating the remaining genetic contribution to MND is crucial for enhancing our understanding of disease and inspiring downstream studies, particularly therapeutic development.

NEWBORN SCREENING

114. GENETICS, NEWBORN SCREENING, AND MIDWIFERY PRACTICE: HOW HAS IT CHANGED OVER THE LAST DECADE?

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Background: Midwives play a role in consent for newborn screening (NBS). In 2011, Victoria implemented a revised protocol including written parental consent for testing and future use, and education program (Charles et al., 2014). **Aim:** To investigate changes in Victorian midwives' understanding and practice of genetics, genomics, and NBS before and after implementation of the revised protocol and education. **Methods:** A piloted survey deployed in 2006 to Victorian members of the Australian College of Midwives (ACM; Bishop, 2010); an updated, online version deployed Sep 2016–Mar 2017. Data analyzed using descriptive statistics. **Results:** In 2006, 317 surveys were completed and 300 in 2016–17 (37.2% vs. 36.1% response, respectively). Nearly half of respondents (42.2% vs. 44.1%) had attended continuing professional development (CPD) in genetics and the majority would attend if offered again (83.5% vs. 86.8%). There was consistently good understanding: that tests require parental consent (98.8% vs. 97.7%), tests are not compulsory (78.8% vs. 94.4%), and how test results are provided (79.4–97.5% across four questions). Knowledge around indefinite card storage was consistently low (51.0% vs. 47.7%) but knowledge about cards given to parents on request improved significantly (24.9% vs. 43.8%; $p = .001$). In 2016–17, 55.5% feel comfortable incorporating genomics into practice, with knowledge being the main barrier. **Conclusion:** Midwives understand the revised NBS consenting process, consistent with information provided to, and by, midwives. There were no significant differences in knowledge of other areas, for example, stored cards use. Midwives appear ready to incorporate genomics into practice with appropriate education.

115. NEXT-GENERATION SEQUENCING IN NEWBORN SCREENING FOR INBORN ERRORS OF METABOLISM: A SIMULATION STUDY

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Background: Many newborn screening (NBS) programs are considering next-generation sequencing for identifying inborn errors of metabolism (IEM) and other conditions. The impact on test accuracy, compared with tandem mass spectrometry (MS/MS), is unclear. **Aim:** To compare screening results generated by targeted NGS with first tier MS/MS screening for IEM. **Methods:** We used phenylketonuria (PKU) and MCADD as case studies. Using retrospective NBS data (2006–2015, $n > 1.38$ million), we quantified the number of true positive and negative screening results. To simulate results of targeted NGS, we scrutinized

the Genome Aggregation Database and ClinVar for known variants of the PAH and ACADM genes (associated with PKU and MCADD, respectively). We used ACMG guidelines to classify genotypes: (1) pathogenic/pathogenic, (2) pathogenic/uncertain significance, (3) pathogenic/benign or wild-type, (4) uncertain significance/uncertain significance, (5) uncertain significance/benign or wild-type, (6) benign or wild-type/benign or wild-type. We calculated expected genotype frequencies using the Hardy–Weinberg equation and compared them with observed screening results. *Results:* Based on MS/MS, 0.04% and 0.02% infants screened true positive for PKU and MCADD. For PAH, the estimated proportions in each category were (1) 8.1×10^{-5} ; (2) 1.3×10^{-4} ; (3) 1.8×10^{-2} ; (4) 4.9×10^{-5} ; (5) 1.4×10^{-2} ; (6) 9.7×10^{-1} . For ACADM, estimates were (1) 6.0×10^{-5} ; (2) 7.6×10^{-3} ; (3) 1.5×10^{-2} ; (4) 1.5×10^{-5} ; (5) 7.6×10^{-3} ; (6) 9.8×10^{-1} . A clear excess of NGS estimated over observed total cases of PKU and MCADD was noted, suggesting an increase in screening false positive rate from NGS alone. *Discussion:* NGS cannot currently substitute for MS/MS and maintain accuracy, so evaluation should address combined/tiered strategies.

PRENATAL DIAGNOSIS

116. DEVELOPING AND IMPLEMENTING THE UPDATED FIRST TRIMESTER SCREENING ONLINE ACTIVITY TO INCLUDE NIPT FOR GPs

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The Centre for Genetics Education (CGE) and RACGP developed a GP online activity on First Trimester Screening (FTS; 2014–2016), which has had high participation, including incorporation into the RACGP Antenatal and Postnatal module. The introduction of Non-Invasive Prenatal Testing (NIPT), absence of NIPT guidelines, and consumer requests for neutral language led to requests from GP education providers and genetic health services for an updated activity. *Aim:* To report on the development and implementation process of updating the FTS activity, and corresponding participation rates. Development involved wide consultation with Antenatal Shared Care GPs (focus group), GP education providers, genetic health professionals, and communication experts. Implementation strategies included promotional material; identifying key contacts in PHNs and GP information sites. Participation rates obtained from CGE, RACGP databases, and website analytics will be reported to July 2017. *Results:* Aspect most requested by GPs included ‘how to talk about NIPT’. Genetic health services recommended the NIPT contingency model and discussing limitations of screening for sex chromosomes. Consumers requested terms to reduce stigma associated with Down syndrome such as ‘chance’ over ‘risk’. Partnership was established with RACGP for updating, shared hosting and promotion to increase GP reach and engagement. The activity, including an NIPT video case study, was launched March 2017. Implementation resulted in links on Primary Health Network (PHN) websites, midwifery programs, integration into GP CPD events and RACGP. GPs face considerable challenges in informing women about FTS and NIPT. Consultation and key partnerships are required for the development and implementation of relevant GP education resources.

117. EXPLORING WOMEN’S EXPERIENCES OF CURRENT AND EMERGING ANTENATAL SCREENING TECHNOLOGIES IN NEW ZEALAND

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Background: In 2010, New Zealand (NZ) introduced government-funded first trimester combined screening (FTCS) to mothers up to 14 weeks’ gestation to determine the chance of their baby being affected with T21, T18, and T13. Recently, non-invasive prenatal screening (NIPS) with reported improvements in detection rate, false positive rate, and positive predictive value has become commercially available, costing users approximately NZ\$600–700. To date, no study has been undertaken to explore women’s current experiences or future thoughts regarding FTCS and NIPS in NZ. *Aims:* To explore women’s knowledge, decision-making, and experiences of FTCS in NZ; and knowledge and perceived usefulness of NIPS. *Methods:* Eight women who received a low-risk screening result after undertaking FTCS in NZ between Jan 2014 and Jul 2015 were recruited directly through e-advertising (Ethics approval: NZ Health and Disability Ethics Committee). To date, semi-structured telephone interviews have been conducted with 7/8 participants by a single interviewer; de-identified transcripts are being coded, with concordance assessed by four independent coders; thematic analysis is guided by an inductive approach. *Results:* A number of preliminary themes and subthemes have been identified: (1) routinization of FTCS screening; (2) perceived value of screening; (3) results bring relief; (4) NIPS timing and accuracy versus cost; (5) more information wanted: online information, written pamphlet, information from Lead Maternity Caregiver, and/or GP. *Discussion:* It is anticipated that outcomes from this research will inform the National Screening Unit as they strive to improve the quality of screening services offered to pregnant women in NZ, and consider the introduction of NIPS.

118. GENDER DISCORDANCE BETWEEN NIPT RESULTS AND ULTRASOUND: A CASE REPORT WITH PRACTICE IMPLICATIONS

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Non-invasive prenatal testing (NIPT) is recognized as the most sensitive method of antenatal trisomy 21 screening, and has been rapidly adopted in Australia in both high-risk and low-risk populations. Although the sensitivity and specificity for aneuploidies other than trisomy 21 is lower, NIPT is commonly used to screen for Trisomy 13, Trisomy 18, and sex chromosome aneuploidies (SCA). There is emerging evidence that the false-positive rate for monosomy X may be particularly high. There are a number of hypotheses to explain this, including maternal, placental, or fetal mosaicism. We report a case where NIPT results were reported as high risk for monosomy X (45, X) in a pregnancy where the fetus was clearly identified as male on ultrasound. The fetus was later found to have a karyotype of 46, X, idic(Y)(q11.22). NIPT, molecular, and cytogenetic data is reported to describe the potential etiology of the discordant NIPT result. Literature on NIPT screening and SCA will be discussed, with a focus on genetic counseling issues and practical implications for services providing NIPT.

119. MICROARRAY IN PRENATAL DIAGNOSIS: 1 YEAR'S EXPERIENCE OF AN ALTERNATIVE APPROACH

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In Australia, microarray has replaced G-banded karyotyping as the first line of investigation in prenatal diagnosis. *Hypothesis:* Restricting prenatal microarray testing to structurally abnormal fetuses would constitute a service that is clinically efficient, cost-effective, and in line with international guidelines. *Method:* The internationally recommended approach of restricting microarray testing to high-risk cases with abnormal ultrasound scan and/or nuchal translucency of more than 3.5 mm was implemented in September 2016. *Results:* Of 270 prenatal specimen received to date for various clinical indications and microarray was indicated and performed only on 52% of cases. Pathogenic copy number changes were detected in six cases and Variation of Unknown Significance (VoUS) were detected in 17 cases. *Discussion:* We review and compare indications and fetal outcome of these cases. *Conclusion:* The clinical and economic impact of the new approach with special emphasis in a public hospital setting will be summarized.

PUBLIC HEALTH GENETICS, ETHICS, AND ECONOMICS

120. GENBREASTCAMOD: A MICROSIMULATION MODEL OF POPULATION-BASED GENETIC SCREENING FOR HEREDITARY BREAST AND OVARIAN CANCER

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Background: Preliminary work on 3,889 cancer-free Australian women has demonstrated the feasibility of population-based genetic screening for breast and ovarian cancer, both in terms of the frequency of actionable mutations (approx. 1%) and the acceptability of the contact process and uptake of Familial Cancer Clinic (FCC) referral. However, the cost-effectiveness of proactive population-based genetic testing compared to the current FCC referral model (reactive genetic testing) has not been assessed. *Aim:* To assess the cost-effectiveness of population-based screening of unaffected women for pathogenic mutations in high penetrance breast and ovarian cancer predisposition genes (BRCA1, BRCA2, PALB2, and ATM) followed by FCC referral compared to current standard practice using a microsimulation model called GenBreastCAMOD. *Overview of model:* We will build the first microsimulation model (GenBreastCAMOD) for assessing the health outcomes and costs of population-based genetic testing for breast and ovarian cancer in a Western population. The base population will consist of 10,000 cancer-free women in the Lifepool prospective cohort attending BreastScreen who will undergo testing and management for breast and ovarian cancer predisposition genes. A counterfactual will be developed as the group who do not have proactive genetic testing. The model will analyze how the increased costs and health outcomes at a family level that come with wider population testing compare to the counterfactual who have not had genetic testing. The model will also incorporate how family history in mutation-positive women compares to current FCC referral guidelines.

121. AUSTRALIANS' PERCEPTIONS OF SUPPORT NEEDS FROM HEALTH PROFESSIONALS FOR INTERPRETATION OF PERSONAL GENOMIC TEST RESULTS

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Background: Australians can order personal genomic tests (PGT) directly from companies online, via medical professionals or alternative health practitioners. PGT results can provide information claiming to inform an individual's health (including nutrition/fitness) and/or ancestry. Surveys of Australian genetic health professionals (GHPs) have shown an increase from 11% (2011) to 51.1% (2017) seeing clients following PGT results, raising concerns about the impact on health services. *Aim:* To explore Australians' interest in PGT and their perceptions of support for result interpretation. *Methods:* An online survey was available to the public from April 2016 (www.genioz.net.au); quantitative data were analyzed descriptively in STATA. Qualitative interviews were also conducted and coded independently using thematic analysis. *Results:* A total of 1,582 Australians fully completed the survey: 19.2% had a medical-/health-related PGT, while an additional 41.0% considered such a test. All respondents were asked about whom they would approach to help them understand their health-related test results: 74.9% selected general practitioners (GPs) (explained further in interviews) and 68.0% selected GHPs. Furthermore, 39.1% selected GPs and 51.5% selected GHPs, even for non-health related tests. *Conclusion:* In our sample, 60.2% Australians have either had or are interested in having a personal genomic test for health-related reasons, including testing for fitness/nutrition. Their views regarding from whom they would seek support to interpret these tests have workforce implications, not only for genetic health services which are traditionally publicly funded with a medical focus, but also for GPs who may have limited understanding of these types of tests and their clinical significance.

122. COST IMPLICATIONS OF FTO GENOTYPE TARGETED LIFESTYLE WEIGHT-LOSS INTERVENTION

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Background: Australia has one of the highest levels of obesity among OECD countries. Personalized nutrition based on genotype profiles offers a potential novel method for addressing obesity. *Research question:* At a population level, is an FTO genotype targeted weight-loss program cost-effective compared to the same program offered broadly to overweight Australian adults? *Methods:* NCD-Mod, an Australian microsimulation model, was used. Counterfactual analysis was based on a weight-loss intervention of high protein diet offered over 2 years. Scenario 1 was offering the intervention to any of the eligible population (Caucasian Australians aged 30–70 years with a BMI greater than 25 kg/m²), assuming 8% uptake of the intervention. Scenario 2 was offering the intervention only to eligible individuals in the population with an FTO rs1558902 AA genotype. The scenario parameters were based on the POUNDS LOST trial reported findings. Key outcomes were reduction in

number of persons with obesity by 2025 and the costs saving to the health system between 2015 and 2025 after a 2-year implementation. *Results:* Approximately 500,000 adults were simulated to complete the intervention in each scenario. The scenario 2 simulated 17,000 less adults with obesity than scenario 1. The additional genetic testing on scenario 2 cost \$166 million (\$10,244 per episode of obesity avoided), health system savings of \$294 million between 2015 and 2025, and a net saving of \$128 million. *Discussion/Conclusion:* A high protein dietary intervention specifically to individuals with FTO rs1558902 genotype AA is potentially cost saving compared to a similar broadly offered intervention.

123. AUSTRALIAN PATIENTS' AND FAMILIES' PERSPECTIVES ON GENOME SEQUENCING

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Background: Genome sequencing (GS) has been introduced into clinical settings in Australia. With the advent of affordable publicly accessible GS services, there is a need to clarify GS perceptions from patients and families affected by diagnosed and undiagnosed genetic conditions, and understand the impact on families. *Aim:* To establish Australian patients and families' perspectives on GS. *Method:* Participants were anyone affected directly or indirectly by a genetic or undiagnosed condition. Two streams of data collection: an online survey of 57 multiple choice questions on financial cost, consent, overall benefit, incidental findings, privacy, and research; and focus group to further explore issues. *Results:* Four hundred eleven participants completed the survey and eight participants attended the focus group; 77% of respondents had high expectations GS would help provide diagnosis, targeted treatments options, and deeper insight into their condition; 73% said GS would have been useful to them in the past to find diagnosis quicker. The majority of respondents (69%, 71%) want to receive incidental findings, even if it is not life threatening. Genetic counselors and clinics are the most trusted sources to get GS done (63%). A total of 52% and 45% of patients are concerned about health and life insurance implications, respectively. *Conclusion:* Patients and families have high expectations of GS. The potential for answers is so powerful, they are willing to overlook potential risks. Genetic Alliance Australia's report lists 21 recommendations for consideration by genomics clinics and testing services. The report details a Patient Charter that is a guide for those considering GS in Australia.

124. COST-EFFECTIVENESS OF CANCER RISK MANAGEMENT FOR BRCA1/2 CARRIERS: EVALUATION OF THE ANNUAL REVIEW PROGRAM

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Women with a pathogenic BRCA1/2 mutation have an elevated lifetime risk of breast and ovarian cancer. Clinical guidelines recommend BRCA1/2 carriers undergo intensive breast screening for early detection, and to consider risk-reducing salpingo-oophorectomy and/or prophylactic mastectomy to significantly reduce their risk. These strategies have been shown to be cost-effective in terms of the cost per life year and quality-adjusted life years (QALYs) saved across multiple settings, provided that there is high to 100% compliance. Existing studies exclude robust consideration of costs associated with the intense clinical follow-up required to ensure women undertake these procedures at an appropriate age. An intensive mutation carrier follow-up program (the Annual Review Program, ARP) has been in place at the Peter MacCallum Cancer Centre and

Monash Health Familial Cancer Centres from 2009 and 2013, respectively, aiming to improve mutation carrier outcomes by providing long-term support. A microsimulation model will be developed in Python to analyze costs, life years, and QALYs over a lifetime horizon for BRCA1/2 carriers participating in a formal ARP compared to standard care (no organized follow-up program). Data from 591 carriers enrolled through a well-established versus newly instituted ARP will be used to populate the model for uptake of risk management recommendations. BRCA1/2 risk management interventions are theoretically cost-effective in reducing mortality and morbidity. Unfortunately, the costs and resource use related to ongoing support and long-term clinical care of these patients is unknown. The proposed evaluation aims to assist in the development of a standard model of health care service delivery for BRCA1/2 carriers.

125. EVIDENCE OF THE COST-EFFECTIVENESS OF WGS IN FAMILIAL INTELLECTUAL DISABILITY

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We are undertaking a study of the economic and social impacts of WGS of familial intellectual disability with the Genetics of Learning Disability (GoLD) service. However, there is little data on the many impacts families face to undertake such a study: financial pressure, relationship strain, poorer caregiver health, and uncertainty about family planning. With advances in genomic testing, families can benefit from an increased diagnostic rate, targeted therapy where available and advice on recurrence, restoring reproductive confidence. Currently, there is no comprehensive economic model of the benefits of genomics for intellectual disability. Typically, health economic models rely on aggregate information, using average patient, costs, and quality of life associated with disease states, do not capture the interrelationship between the health of one individual and others in a family, and the costs captured are generally limited to the health system. Our multidisciplinary team designed a series of questionnaires to capture the large and diverse health, social, and economic impacts of intellectual disability taking into account impacts within and beyond the health system, and the multi-person and intergenerational impacts. These questionnaires capture detailed information on the proband and primary caregiver, including costs of testing and treatment, quality of life, employment, welfare, family planning, education, relationship strain, and social connectedness. The data from these questionnaires will be used to develop the world's first micro simulation model capturing the diverse and inter-related policy impacts for state and federal government, including the health and social costs at the individual and population level.

126. WITHDRAWN

127. SEVEN CHALLENGES ASSOCIATED WITH THE ETHICAL GOVERNANCE OF [GLOBAL] HYBRID GENOMIC DATA INFRASTRUCTURES (GENOMIC BIOBANKS)

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It is reasonable to expect that contemporary genomic biobanking governance arrangements should be developed to respect humans and non-human animals, promote fair distribution of benefits,

foster trust, reciprocity, and integrity while offering support to the advancement of research and scientific knowledge. If governance is inclusive, sustainable, and responsive to current and future scientific developments, then it is likely to be practically useful and ethical. Many will benefit. In this presentation, seven key challenges associated with the ethical governance of new [global] hybrid genomic data infrastructures (genomic biobanks) will be identified and briefly analyzed. These include (1) the lack of consistent (universal) data terminology across different jurisdictions; (2) the diverse range of different understandings of privacy, confidentiality, and consent across cultures and legal traditions; (3) the different perspectives about the nature and role of data information pathways; (4) the importance of understanding diverse experiences of 'place' and respecting and capturing Indigenous experiences; (5) the relationship between genetics, genomics, data science, and decision-making within governance frameworks; (6) deciding how best to facilitate social justice; and (7) determining how to address current lack of broad community engagement in genomics. The Australian context is used as an initial focus for discussion. However, the claims and suggestions are applicable anywhere. They are particularly pertinent to situations where the scientific reliance on new hybrid genomic data infrastructures is outpacing considered ethical analysis.

128. ESTIMATING THE EDUCATION COST IMPACTS OF WHOLE EXOME SEQUENCING FOR INFANTS WITH SUSPECTED MONOGENIC DISORDERS

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Aim: To estimate the potential impacts on education cost outcomes to the Commonwealth and State Government of Victoria of early genomic diagnosis and targeted intervention. **Methods:** A budget impact assessment was conducted using Commonwealth and State per-student-funding data. The model was developed using outcomes from genomic testing, relevant literature, and projected educational costs for a cohort of 80 infants with suspected monogenic disorders who underwent WES early in the clinical trajectory. Modeling was undertaken to account for the potential impacts and uncertainties arising due to the complex nature of rare genetic disorders, uncertainty regarding natural history and treatment outcomes, and the inherent uncertainty in forecasting lifetime costs. **Results:** Educational costs differ substantially at different levels of disability, ranging from \$23,132 to \$67,780 per year per student. However, preventing progression to severe intellectual disability in one case can be estimated to save \$724,644 to the education system over 13 years of schooling (Prep to year 12), illustrating that early diagnosis can result in substantial education costs or savings. The full model will be presented, demonstrating the potential impacts and uncertainties. **Discussion:** Although early genomic diagnosis would not be expected to alter educational outcomes in most children tested, some neurometabolic conditions are potentially amenable to treatment that would alter the natural history of the condition. This analysis demonstrates that the health sector costs of WES can be far outweighed by budget implications in other sectors, with education being just one such example.

129. THE MELANOMA GENOMICS MANAGING YOUR RISK STUDY: A PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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Background: Our pilot trial ($n = 118$) found that delivering information on personalized genomic risk of melanoma to the public is acceptable and feasible as a potential melanoma prevention strategy. **Aim:** To conduct a large-scale study to evaluate the efficacy, stratified by phenotypic risk (low, high), of giving information about personal genomic risk of melanoma (common variants in 21 genes) in reducing exposure to ultraviolet radiation measured objectively at 12 months. **Methods:** Participants ($n = 944$) will be recruited from the general population, and randomized to either (1) (intervention arm) provide a saliva sample, receive personalized melanoma genomic risk information, telephone genetic counselor call, and educational booklet on melanoma prevention; or (2) (control arm) the same educational booklet only. At baseline, 1- and 12-month time-points, we will examine sun protection and skin-examination behaviors, psycho-social outcomes, and ethical considerations surrounding offering genomic testing at a population level such as non-directiveness. A within-trial and modeled economic evaluation will be undertaken facilitated by linkage to administrative data. **Results:** Our pilot trial showed non-significantly reduced objectively measured sun exposure for intervention versus control groups (-16% standard erythemal doses per day, 95% confidence interval — 43% to 24%) and no evidence of adverse psychological outcomes. Sample size calculations for the large study are based on detecting a 20% difference in each phenotype group. **Discussion:** This novel, comprehensive study will address ethical, psycho-social, and economic aspects related to providing this information, to help understand the broader impact of the intervention and to give insight into any behavioral effects.

130. REVIEW OF THE UTILITY AND THE COST-EFFECTIVENESS OF NEXT-GENERATION SEQUENCING TECHNOLOGY IN CANCER CARE

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Background: Clinical effectiveness and cost-effectiveness of the application of next-generation sequencing (NGS) is important in assisting policy makers to allocate scarce financial resources. Our review provides critical assessment of the integration of NGS into cancer care. **Aim:** The aim of this study is to review the evidence of clinical and cost-effectiveness of applying NGS technology in cancer care. **Methods:** We systematically searched for articles on clinical effectiveness and cost-effectiveness of NGS in cancer care from Medline, PubMed, and EMBASE, from 2011 to 2016, and performed a systematic review of those articles. Statistic analysis

was performed. **Results:** In the evaluation of the effectiveness of NGS, 42 articles reported sequencing patients samples using a targeted gene panel, 76.36% (range = 30.56–100.00) of the successfully sequenced patients harbored at least one mutation and 57.94% (range = 15.87–100) harbored actionable mutations. Only four articles reported an economic assessment of the application of NGS in cancer care. In general, application of NGS in planning cancer treatment was reported to be cost-effective. However, NGS was not found to be cost-effective when used to direct targeted treatment in metastatic lung adenocarcinoma. Factors with a significant effect on the incremental cost-effectiveness ratio are the Quality-Adjusted Life Years gained from detecting actionable mutations through NGS, the probability of identifying actionable mutations, and the cost of the NGS assay. **Conclusions:** While there is some evidence that application of NGS in cancer care could be cost-effective, further evidence of the cost-effectiveness of the application of NGS in cancer care is warranted.

131. 'YOU DOWNLOAD YOUR GENOME ...': EXPLORING HOW AUSTRALIANS USE INFORMATION FROM PERSONAL GENOMIC TESTING

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Background: Personal genomic testing (PGT) gives individuals access to information for health and 'recreational' purposes, like ancestry and sporting ability, and is marketed in Australia. PGT may be purchased directly by consumers online; services may include the option to download raw data. **Aim:** To explore how Australians report using information obtained from PGT ordered online. **Methods:** An online survey was available from April 2016, and advertised through social media, community, and professional groups and researchers' networks. In-depth qualitative interviews were conducted and coded independently using thematic analysis. **Results:** A total of 2,047 Australians have attempted the survey, with 1,582 fully completing; 75.8% were female, 72.7% had some university education, and 10% reported a professional background in genomics. A total of 479/1,725 individuals (27.8%) reported having genetic testing, of whom 179 ordered testing online only. The most common tests ordered online only were ancestry (98.3%), personal characteristics (20.2%), relationship/identity (19.1%), and carrier status (16.2%). Respondents reported using ancestry results to add information to family knowledge (81.1%) and to trace relatives (71.4%); relationship-testing results were also used to contact relatives (88.2%). Conversely, most respondents did nothing with personal characteristic results (91.7%) or carrier results (58.6%). Interviewees discussed using raw data to conduct further analysis with online programs, sometimes beyond their original reason for testing, including for health. **Conclusion:** Individuals who had online PGT report using their information in different ways, including opportunistically seeking further analysis. The availability of publicly available open-access online tools may affect health professionals who are requested to provide support around interpreting this information.

132. INTEGRATED GENETIC ANALYSIS: HARNESSING THE POWER OF NGS

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The advent of next-generation sequencing (NGS) has revolutionized clinical genetic testing. Empowered by NGS technologies, clinical genetics has transitioned from single gene analysis to multi-gene panels, exome sequencing, and emerging genome sequencing. Still, chromosomal analysis remains the first line of genetic testing for multiple conditions. Chromosomal analysis is well established in the clinic, with multiple applications, including prenatal, postnatal, and somatic testing. While karyotyping is still the gold standard for genome-wide analysis of large rearrangements, with or without net gain or loss of genetic material, the study of copy number variants is often equated to microarray platforms. While it is clear that microarray analysis is an appropriate tool to detect genetic imbalances, it presents some challenges that might be overcome by NGS technologies. Here we propose an NGS-based approach to chromosomal analysis that exhibits increased sensitivity with an unbiased representation of the whole genome. Taking advantage of NGS, we present pair-ended, low-coverage whole genome sequencing as an alternative to microarray testing. We tested 31 samples from cell lines and 19 de-identified controls, using a standard microarray platform (4×180 K copy number variant and SNP custom array with a resolution of 1 kb in selected disease genes, up to 50 kb in OMIM genes, and 150 kb in the rest of the genome) and low-coverage whole genome sequencing. All copy number variants identified by the microarray platform were detected by the NGS-based approach, while additional 46 and 6 copy number variants in the cell lines and control individuals, respectively, were identified by the NGS-based approach only. All the identified variants were verified by orthogonal methods. Compared to microarray analysis, the NGS-based test exhibits increased sensitivity, with a detection limit of up to 200 bp when average sequencing coverage is 1× and identifying exact break points when higher coverage is used. In addition, NGS-based chromosomal analysis allows the identification of structural abnormalities that microarray is unable to detect. While up to now, karyotyping has been the only tool available to identify balanced translocations, NGS-based chromosomal analysis allows the positional reconstruction of the genome, revealing possible gene fusions and other balanced chromosomal aberrations. Moreover, primer design for segmental duplication, a critical mechanism of evolution, is extremely difficult for areas of high homology, increasing the probability of missing variants in this region when using a primer-based technology such as microarray, MLPA, or qPCR. In contrast, a combination of NGS-based chromosomal analysis and stringent bioinformatic protocols, allows correct mapping of reads with up to one base difference in 300 bp DNA block (~99.7% identity) correctly computing CNVs in areas of segmental duplication. More than half of CNVs discovered in this study were located in duplicated regions. Considering the pace and the direction in which clinical genetic testing is moving, integrated testing options might be an appropriate target for the new generation of genetic tests. While microarray analysis is an independent platform, NGS-based approaches can be integrated in a step-wise testing algorithm that could result in a cost and time effective alternative to current strategies. Thus, NGS constitutes a suitable technique to chromosomal analysis in the post genomic era.