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Plenaries and Orals

Plenary 1
INTEGRATING HIGH THROUGHPUT GENOMIC DIAGNOSTICS WITH HEALTH CARE: GENOMICS ENGLAND

Mark Caulfield

Plenary 2
INTEGRATING GENOMICS INTO CLINICAL PRACTICE: THE AUSTRALIAN GENOMICS HEALTH ALLIANCE

Kathryn North AM[1,2,3]
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Next-gen sequencing is already transforming the diagnosis and management of genetic disorders. However, effective integration of this 'disruptive technology' into everyday clinical practice will require a whole-of-system approach that builds on existing expertise. In Australia, we also need to overcome the 'state/federal divide' in the funding of genetic testing to develop a cohesive national approach that is cost effective and provides equitable access. The Australian Genomics Health Alliance (AGHA) is an NHMRC-funded national network committed to implementing genomic medicine within Australia and providing evidence to inform policy and practice. AGHA comprises 47 partner organisations including the diagnostic pathology and clinical genetics services of all Australian States and Territories, along with the major research and academic institutions and peak professional bodies. By approaching clinical genomics at a national rather than state-based level, we increase our critical mass and offer a single point of contact for government and for national and international consortia. Our approach — starting with the patient and developing a system that is focused on improving patient care and outcomes — provides us with a unique opportunity to lead internationally in the integration of genomics into healthcare.

Plenary 3
INTEGRATING THE GENOME AND THE PHENOME: A NEW PLATFORM FOR HEALTHCARE

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The use of massively parallel sequencing for accurately diagnosing disease is becoming increasingly routine in clinical practice. As the cost of sequencing continues to decrease, larger numbers of genes are examined as part of a single test. Indeed, it appears inevitable that sequencing costs will reach a point where sequencing the entire genome will be more practical than sequencing subsets of it. Apart from the capability to diagnose greater numbers of diseases in a single test, one of the other repercussions of this trend is that increasing amounts of information become available for understanding the basis of disease for which there is no clear diagnosis. Although this data can be collected at almost no cost, the value of this information can only be fully realized with associated phenotype data. Existing medical information systems are not structured in a manner to allow integration of genomic and phenomic data, and as a result there is currently no means by which to derive new associations between genotype and phenotype from clinical data. In this presentation, I will describe the clinical framework that we are implementing as a pilot at the Kinghorn Centre for Clinical Genomics, which aims to mutually benefit both individual practitioners, through increased diagnostic yields, and researchers, through integrated access to genomic and phenomic information. We propose that this model, the utility of which grows with increasing participation, could be extended into other clinical genetic settings and ultimately become part of a standard platform for healthcare.

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Plenary 4
EXPERIENCE FROM 10,000 DIAGNOSTIC EXOMES

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We are using exome sequencing in clinical diagnosis for a broad range of diseases. For the year 2016, we expect to run 8,000 diagnostic exome tests. We have reviewed our experience of the first 10,000 exome tests, and find that this has now become an integrated part of modern medical care for patients with rare diseases. After 5 years of experience with exomes in a clinical setting, the following conclusions are drawn:

- Exomes do better than doctors most of the time.
- Exomes do not generate large numbers of incidental findings.
- Incidental findings can be managed by a combination of careful informed consent, targeted analysis where possible, and informed genetic counseling.
- Genomes do better than exomes, but not much at this point.
- We do not understand enough of non-coding DNA to allow easy detection of variants that impact disease.
- We find similar mutations for seemingly distinct neurodevelopmental disorders, suggesting broad clinical heterogeneity, and fueling nosological debate.
- De novo mutations are an important cause of severe genetic disease in non-consaguineous populations.

Plenary 5
PEDIATRIC GENOMES — TECHNOLOGY, SCIENCE AND EMOTION

Sarah Bowdin
Hospital for Sick Children, Toronto, Canada

The ability to sequence and interpret an individual genome is a technological and scientific breakthrough of massive proportions. Physicians are now introducing this transformative technology to clinical care, which brings huge responsibilities both to our patients and to the healthcare systems within which we operate. In order to pilot the implementation of pediatric genomic medicine, we developed the SickKids Genome Clinic, a multidisciplinary research project that conducts whole genome sequencing (WGS) for children who are undergoing genetic evaluations. WGS was chosen given the potential to capture all classes of genetic variation in one experiment. The Genome Clinic team is composed of clinical geneticists, genetic counselors, molecular and cytogeneticists, ethicists and health economists, with design input from computational medicine and bioinformatics. The clinic allows us to study outcomes beyond the diagnostic rate of WGS, including the impact of actively searching for predictive secondary variants in the pediatric population, healthcare utilization following WGS, and the new work flows demanded by this technology. We have approached 321 families to date, with 54% agreeing to participate. With parents' permission, we systematically search children's genomes for diagnostic variants that explain the patient's known phenotype and predictive secondary variants (PSVs) associated with occult or future disease. WGS identified genetic variants meeting clinical diagnostic criteria in 34 of the first 100 cases, including four subjects with two distinct genetic diagnoses. Each facet of this study has provided new insights into how WGS can be safely and effectively integrated into clinical medicine, and this talk will highlight the team's most important learning experiences to date.

Plenary 6
RETURN OF RESULTS FOR MYOCILIN GLN368TER

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Aim: Population-based genetic screening for glaucoma is not yet recommended. Screening for glaucoma mutations from array and sequencing data might be viable. Myocilin has been known as a genetic cause of primary open angle glaucoma for nearly 20 years. Cascade genetic screening of other family members is standard of care in families with myocilin glaucoma. The most commonly found mutation in Europeans is Gln368Ter, present in approximately 1/500 people of European ancestry and shows a strong founder effect. We identified a SNP haplotype that could impute the mutation with high sensitivity and specificity. *Method:* We reviewed the frequency of the founder haplotype in different human populations and the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG). *Results*: The haplotype associated with Gln368Ter is common and at similar frequencies across most European populations. Thus imputing Gln368Ter from arrays of European derived cohorts would be viable.Gln368Ter accounts for 25 of 1200 (2%) of advanced glaucoma cases from ANZRAG. *Discussion*: Myocilin mutations can be identified from whole exome sequencing data and accurately imputed from most GWAS studies. Consideration that these results should be returned to participants is required. The treatable nature of glaucoma and the implications for other family members make this an important consideration if we are to attempt to reduce glaucoma blindness. Given the 'lack of consent' in screening clinically for glaucoma, there would appear to be no difference in feeding back this genetic risk to patients who have had a genetic test for any eye disease.

Sutherland Lecture
MEDICINE IN THE TIME OF GENOMICS: FROM DIAGNOSIS TO TREATMENT

Ravi Savarirayan
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Quantum advances have occurred in human genetics since Watson and Crick proposed a structure for the salt of deoxyribose nucleic acid (DNA). These culminated in the human genome project, which opened myriad possibilities, including *individualized genetic medicine*; medical advice, management, and therapy tailored to a specific genetic constitution. Advances in genetic diagnostic capabilities have been rapid, and the genome can now be sequenced for several thousand dollars. The enhanced ability to molecularly confirm a suspected genetic diagnosis is having profound impacts on clinical medicine for single gene and complex disorders alike. It has allowed further insights into pathogenesis of genetic disease and, crucially, the identification of precision intervention targets. If we are to move swiftly to an era of 'bespoke' medicine, it is vital that effective, quick, and robust pathways are established leading from identification of key clinical, biochemical, and molecular hallmarks of a genetic condition to biologically plausible intervention points. This will require effective liaison between clinicians, basic scientists, consumers, funding bodies and industry, and employ animal and cellular models as proof-of-principle with well-designed human clinical trials that include appropriate functional endpoints. This 12th Sutherland lecture will use inherited disorders of cartilage and bone (*skeletal dysplasias*) as a rare genetic disease template to illustrate the journey from accurate diagnosis and natural history delineation to pathogenesis-based therapies based on animal models, and delivered via human clinical trials. It will also outline research aimed at enabling equitable access to these new disease-modifying

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and life-changing treatments in all populations, including Indigenous Australians.

Plenary 7
THE RETURN OF MEDICALLY ACTIONABLE SECONDARY FINDINGS IN THE UNITED STATES: WHO GETS TO CHOOSE FOR THE FAMILY?

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For biomedical research involving minors, parental permission replaces consent as the primary way to protect children from potential harm. Adolescent participation via assent, though, is critical to the ethical conduct of biomedical research. Pediatric genomic sequencing challenges classic notions of autonomy and assent because findings may have significant health implications for the teen's family members. Consequently, conventional approaches to achieving consent for health research may be insufficient to the risks, benefits, and possibilities offered by genomic sequencing. This research focused on describing the content of informed consent interactions to discover how best to encourage, support, and nurture adolescent participation in genomic sequencing. Our team offered whole exome sequencing to patients from five pediatric disease cohorts at an urban teaching and research hospital in the United States. Twenty-five adolescents aged 12–19 and their parents completed informed consent sessions with study clinicians. Researchers used grounded theory techniques to analyze session content and processes. Adolescent participants were briefly vocal when asked direct questions. Otherwise, they mostly stayed quiet. Parents functioned as protectors and information-holders, particularly when adolescents felt unprepared to make decisions. Clinicians used proscriptive language to direct families to consider adolescents' expressed preferences, to balance the interests of multiple caregivers, and to give families time to consider their options before making decisions. In two cases of significant family disagreement, providers maintained a non-directive stance towards all parties, and then excused themselves from intense discussion by deferring decisions to a later date. Adolescents with ongoing health conditions may have complex caregiving relationships with caregivers and clinicians that support dependency during a developmental period marked by an increasing drive towards interdependence. Rather than target adolescent autonomy, enhancing the agency of adolescents in decision making may more appropriately address their needs so that all stakeholders provide input and are respected throughout the informed consent process.

Plenary 8
IMPLEMENTING GENOMICS IN THE CLINIC: A COLLABORATIVE APPROACH

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Implementing genomics into healthcare practice requires change across the healthcare system. The Melbourne Genomics Health Alliance is addressing this challenge by taking a collaborative approach across 10 independent healthcare, research and academic organisations and 'starting with the patient and working backwards' to embed change. In order to build genomic capability, evaluate the impact of genomic sequencing and identify how it can best be delivered, a 2-year demonstration project was conducted. More than 300 patients were offered whole exome sequencing (WES) in parallel with standard care by clinicians. Patients had one of five clinical indications, enabling condition-specific and common approaches to be identified. Clinicians from six disciplines and genetic counselors provided pre- and post-test counseling. Common systems, tools and policies were developed and applied across the participating hospitals and laboratories. Evaluation data were collected through clinical records, participant surveys and interviews with 32 clinicians and 14 other stakeholders. Impact evaluation included the rate of detection and resulting change in patient management. The evaluation of processes encompassed data sharing, patient selection, consent, genetic counseling and clinical interpretation. The impact of involvement on clinicians was also explored. The results of this comprehensive evaluation are informing implementation of systems locally that meet the needs of both the workforce and patients. Crucial insights will be provided into the aspects of clinical practice which will need to alter to progress the introduction of genomic medicine.

Plenary 9
INTEGRATING GENETICS SERVICES INTO PAEDIATRIC CANCER CARE. WHAT DOES THE FUTURE HOLD?

Claire E. Wakefield[1,2*], B. C. McGill[1,2], E. J. Doolan[1,2], G. Georgiou[1,2], J. E. Fardell[1,2], C. Signorelli[1,2], K. Tucker[3,4], A. F. Patenaude[5], R. J. Cohn[1,2]

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Background: Little is known about genetic testing, genetics-related beliefs, and acceptability of genetics services in childhood cancer survivors and their parents. This presentation will describe the largest series of genetics services studies undertaken in pediatric oncology in Australia and New Zealand. *Method:* 1,215 individuals participated (385 survivors, 190 parents, 429 age/rurality-matched young-person controls, 211 parent controls). Participants completed questionnaires and optional interviews. Quantitative data were analysed with SPSS20. Qualitative data were analysed with NVivo11. *Results*: 7.2% of survivors had been offered cancer-related genetic testing (80% consented). In survivors and their parents, 'bad luck/chance' was the most commonly endorsed belief regarding the cause of childhood cancer (71.8%), followed by environmental (30.3%) and then genetic (15.8%) attributions. Controls were more likely to endorse genetic causes ($p < .01$). Despite endorsing access to genetic services and information as 'important/very important', many reported unmet genetics information needs (survivors: 40.3%; parents: 43.1%). Survivors and parents described positive attitudes towards two new genetics technologies (genetic testing to determine survivors' risk of developing late side effects and using patient-derived xenografts to test potential treatments for newly diagnosed children). Perceived benefits outweighed negatives, and most participants reported that they were willing to pay, and wait, for these services. *Conclusion*: Childhood cancer survivors and their parents have substantial unmet needs regarding genetics information/services. Though clinical efficacy is yet to be clearly demonstrated, they describe positive interest in new genetics services. Individuals in the general community appear more cautious, possibly because they have not personally experienced the impact of childhood cancer.

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Plenary 10
BACK TO THE FUTURE — A PERSONAL REFLECTION OF THE DEVELOPING PROFESSION OF GENETIC COUNSELING IN AUSTRALIA

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This presentation is a personal reflection of the experience of developing the profession of genetic counseling in Australia, and subsequently establishing student education at a masters level. Genetic counseling is a relatively new profession first established in the United States in the 1940s. In Australia, the first discussions occurred at HGSA meetings in the 1980s. Several professional groups had an interest in this process, including clinical geneticists, scientists, social workers, and nurses in existing roles in genetic services. The first official meeting occurred in 1989, with the author appointed as 'a person with counseling expertise'. Official guidelines and certification were developed in 1990. These original guiding principles remain as the key competencies of the profession. From these beginnings, training programs were established — some in house (at the Victorian Clinical Genetics Service), with the first Graduate Diploma of Genetic Counseling established at Newcastle University in 1995. This was followed by the University of Melbourne program, in 1996.The development of this program into a 2-year masters-level program is discussed, with reference to the ongoing challenges of developing curriculum, modes of teaching, and the overall philosophy guiding student education. A glimpse into the future of genetic counseling will be offered.

Plenary 11
NOVEL THERAPIES IN CONGENITAL DISORDERS OF GLYCOSYLATION

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Although the number of subtypes are exponentially growing, curative treatment is still not available in most types of congenital disorders of glycosylation (CDGs). Oral monosaccharide therapy has been shown to be clinically efficient in different types of this intriguing inborn error of metabolism, including MPI-CDG and SLC35A2-CDG. We evaluated the possible efficiency of monosaccharide therapy using galactose treatment in 16 patients with different types of CDGs evaluating their fibroblasts by glycomics, ICAM1 immunohistochemistry and Western blot analysis. The patients also underwent a dietary protocol of incremental increase of oral galactose treatment with increase of the dosage from 0.5g/kg/day to 1.5g/kg/day every 6 weeks to a maximum dose of 50g/day, followed by clinical and laboratory investigations. Glycane analysis, immunohistochemistry and protein expression of ICAM1 in defective cells confirmed the severe glycosylation defect. Galactose supplementation added to the cell culture led to significant improvement of N-linked glycosylation in 5 days. Galactose concentration between 0.75mEq and 2mEq were the most effective. Higher dose galactose concentrations (5-10 mEq) inhibited glycosylation. The monosugar supplementary therapies affected both ER and Golgi function and increased mannosylation, galactosylation and sialylation in patients both in vitro and in vivo. Laboratory evaluations on oral galactose supplementation showed improving endocrine liver and coagulation parameters during the clinical trial. Galactose was well tolerated, without side effects.

Plenary 12
NOVEL GENOME ENGINEERING TOOLS BASED ON CRISPR-CAS SYSTEM AND THEIR APPLICATION AND INTERSECTION WITH GENOMICS ANALYSIS

Le Cong
Broad Institute of MIT and Harvard, Massachusetts Institute of Technology, Cambridge, MA, USA

Advances in genome sequencing and related technology have led to unprecedented pace at which we can identify genomic and epigenomic changes associated with human health and disease. Nonetheless, due to the vast number of variants under investigation, validating their biological functions and exploring them as potential drug targets remain extremely time and cost consuming. The ability to quickly and accurately assess these candidate variants is essential to the goal of precision medicine. For this purpose, genome editing tools adapted from CRISPR-Cas system can be employed for modifying DNA sequences at genome scale with minimal expenses. I discuss here how genome engineering technology can be deployed as versatile discovery tool. I will focus on the power and precision of novel technology development and describing its potential therapeutic application. In addition, I will highlight the emerging trend on how computational analysis could be integrated with new generation of molecular tools to transform our ability to connect genotype with phenotype for treating human diseases.

Plenary 13
NANOPARTICLE-MEDIATED TRANSFER FOR THE TREATMENT OF MUCOPOLYSACCHARIDOSES

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Nanotechnology has represented in the last year a very promising approach for the delivery of therapeutic molecules across the blood-brain barriers. For this reason, we have investigated whether they may be used to contrast the progression of the CNS alterations typical of the neuronopathic phenotype present in patients affected by lysosomal diseases (LSDs). LSDs are a group of metabolic syndromes, each one due to the deficit of one lysosomal enzyme. Many LSDs affect most of the organ systems and overall about 75% of the patients present neurological impairment. Enzyme replacement therapy, although determining some systemic clinical improvements, is ineffective on the CNS disease, due to enzymes' inability to cross the blood-brain barrier (BBB). With the aim to deliver the therapeutic enzymes across the BBB, we here assayed biodegradable and biocompatible PLGA-nanoparticles (NPs) in two murine models for LSDs, Mucopolysaccharidosis type I and II (MPS I and MPS II). PLGA-NPs were modified with a 7-aminoacid glycopeptide (g7), yet demonstrated to be able to deliver low molecular weight (MW) molecules across the BBB in rodents. We specifically investigated, for the first time, the g7-NPs ability to transfer a model drug (FITC-albumin) with a high MW, comparable to the enzymes to be delivered for LSDs brain therapy. In vivo experiments, conducted on wild-type mice and knockout mouse models for MPS I and II, also included a whole series of control injections to obtain a broad preliminary view of the procedure efficiency. Results clearly showed efficient BBB crossing of albumin in all injected mice, underlying the ability of NPs to deliver high MW molecules to the brain. These results encourage successful experiments with

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enzyme-loaded g7-NPs to deliver sufficient amounts of the drug to the brain district on LSDs, where exerting a corrective effect on the pathological phenotype.

Plenary 14
LIVER-TARGETED GENE TEHRAPY FOR UREA CYCLE DISORDERS

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Exciting developments in AAV vector technology and success in the treatment of neonatal lethal urea cycle defects in mice (OTC and ASS deficiency) by gene therapy, bode well for human translation. As with all gene therapy trials, potential success is fundamentally dependent upon accurately approximating the reach of the chosen gene transfer technology with the demands imposed by the pathophysiology of the target disease and biology of the target organ. Experimental studies of liver-targeted gene therapy in urea cycle deficient mice, mathematical modeling and lessons from nature provide insight into the gene transfer efficiencies required, and suggest that the hepatocyte transduction levels needed for therapeutic benefit in severe OTC deficiency could be in the order of 20%. This target is plausibly achievable with emerging AAV vector technology, but will require careful vector optimization, including selection of the most human tropic capsid available. In the developing liver, loss of episomal vector genomes over time, as a consequence of hepatocellular proliferation, will also need to be considered in configuring an early phase trial. While potentially subject to debate, a 'bridge- to-transplant' trial for infants and children with severe disease ffers a realistic prospect of therapeutic benefit while accommodating possible risks.

Plenary 15
DEVELOPMENT OF NOVEL GENETIC THERAPIES FOR HAEMOGLOBIN DISORDERS

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The β-thalassemias, sickle cell disease (SCD) and hemoglobin E (HbE) disease represent the most important hemoglobinopathies from a clinical point of view, causing severe morbidity and mortality worldwide. Current standard of care involves life-long regular blood transfusions and iron chelation therapy to reduce iron toxicity. The transfer of gene-corrected autologous hematopoietic stem cells (HSCs) could provide a therapeutic alternative, as recent lentiviral gene therapy trials have demonstrated. The greatest caveat in the use of integrating lentiviral vectors lies in the inability to control the site of integration, which can potentially cause genotoxicity. This issue has driven the search for safer gene therapy approaches. One possible solution is to target the integration of a therapeutic gene into a genomic 'safe harbour' site that supports long-term transgene expression. Alternatively, genome editing could be used to correct patient HSCs ex vivo. Ideally, correction of the β-globin gene in HSCs could be achieved through homology-directed repair (HDR), resulting in the production of healthy erythrocytes. Several studies including work from our group have shown that the human β-globin locus is amenable to genome editing. However, technical limitations and safety concerns need to be overcome for this novel approach to become clinically feasible. Here, we highlight recent developments and important new directions in β-thalassemia and SCD gene therapy.

HGSA Oration
LINKS AND SECOND CHANCES

Agnes Bankier
Royal Childrens Hospital Human Research Ethics Committee, Royal Children's Hospital, Melbourne, VIC, Australia

This year we celebrate 40 years of the HGSA. I have been privileged to share 35 of those years, in many leadership roles. This period has seen exciting advances in human genetics. Parallel with these has been the development of clinical and diagnostic genetic services, emergence of clinical geneticists and genetic counselors as recognised professions, and a broad range of ethical and translational challenges from scientific discovery to clinical practice. The growth and maturity of the HGSA, its special interest groups, accreditation bodies and advisory groups have paralleled this development. As Honorary Archivist to the HGSA, it has been a joy to review the original documents and see how much we achieved. The Oration has been an opportunity to also reflect on my genetic journey and my time as Director of the VCGS. Victoria, through the vision of the late David M. Danks and development of clinical services by John G. Rogers and others, led the way, training the first clinical geneticists in Australia. This year we celebrated 40 years of newborn screening. We could also celebrate the advances in our diagnostic services and Possum. Possum has been a great project. Developed in 1984 as an aid for the diagnosis of children with patterns of birth defects, it was the first to combine computerized information linked to images on a videodisc. Its early development was very exciting. Over the past 30 years Possum has undergone several technological transformations. Now web-based, Possum is known and valued internationally. And second chances? That is about opportunity and gratitude … to be elaborated.

Plenary 16
APPLICATION OF DISEASE REGISTRIES IN CLINICAL PRACTICE AND RARE DISEASE RESEARCH

John McNeil
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Clinical registries have been established across a range of diseases in order to monitor quality of care, establish the safety of drugs devices and new interventions, and to support research. In the case of rare diseases registries are particularly valuable because they provide information about the epidemiology of a condition, and to facilitate various forms of clinical research. The essential feature of a clinical registry is the collection of an identical dataset from patients at each site where they are treated. Typically, the enduring data is kept to a minimum but additional information is added when necessary, typically for a limited time or from a minority of specialist hospitals. Another common feature is the systematic collection of outcome data at identical times after treatment using standard definitions. The data is sent to a central custodian responsible for amalgamating and interpreting the information. Registries are increasingly focusing on the collection of biomarkers at the time of registration. These samples are important for the identification of new markers of prognosis or of response to treatment. They are also being seen as a potential infrastructure for clinical trials. In this way registries are starting to provide a 'missing link' that will enable more rapid evaluation and approval of new drugs and other treatments. Despite the obvious value of registries for facilitating clinical research, the success of new registries depends particularly on matters such as governance and funding models. In this presentations, these issues will be discussed in detail, accompanied by an update on progress with rare disease registries in the United States, United Kingdom, and Europe.

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Plenary 17
INTERNATIONAL PEDIATRIC SURVEILLANCE UNITS CONTRIBUTING TO RARE DISEASE REGISTRIES

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There are 11 pediatric surveillance units across the world, dedicated to collecting population-based data about children with rare diseases. Together, they form the International Network of Paediatric Surveillance Units (INoPSU). Each national unit collects cases diagnosed according to standardised criteria and protocols including diagnostic features, complications, treatments and outcomes. We estimate that a total of 12,000 pediatricians and child health specialists across the 11 units by responding to monthly surveillance report cards that list selected rare childhood diseases. This surveillance methodology has been adapted in some countries to include a patient consent process to support disease registries; for example, Australian Rett Syndrome Registry (Aussie-Rett), British Paediatric Orphan Lung Diseases (BPOLD) registry, Australian Registry Network for Orphan Lung Diseases (ARNOLD), the Portuguese Cerebral Palsy Register. The Australian Paediatric Surveillance Unit is currently working towards establishing a registry for fetal alcohol spectrum disorders. Detailed registry data including demographics, diagnostic features and tests, treatment and outcomes are collected for each case via a secure online portal. Cases are reported prospectively, by specialist clinicians, according to standardized case definitions, to ensure high level of data quality, timeliness and completeness. There is potential for data sharing and comparisons internationally, and the registry platforms, once established, can support basic research, clinical research, longitudinal studies and clinical trials. There is also potential for data linkage with other data collections to assess educational outcomes, economic impact and social inclusion.

Plenary 18
REGISTRIES FOR RARE RESPIRATORY DISEASES

Adam Jaffe[1]

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In Australasia, there is limited capacity to measure the impact heath care makes on the outcomes of patients with rare respiratory diseases in line with best evidence. Clinical registries for patients with rare respiratory diseases enable a systematic approach to serve a scientific, clinical or policy purpose. There is a growing interest in the use of clinical quality registries for rare respiratory diseases in Australasia. These registries may be single disease focused — for example, the Australian Cystic Fibrosis Data Registry (ACFDR), the Australian Idiopathic Pulmonary Fibrosis Registry and the Australian Bronchiectasis Registry — or focused on gathering prevalence data on multiple rare respiratory diseases — for example, the Australasian Registry Network for Orphan Lung Disease (Casamento et al., 2016 *Journal of Rare Diseases, 11*:42). Single disease registries, such as the ACFDR, allow detailed analysis of health outcomes of patients with CF in Australia and are published annually. Recently, the health outcomes of each CF center have been published transparently, thus allowing intercenter comparisons, as well as international benchmarking (Martin et al, 2012, *Pediatrics 129*: e348-345). This transparent benchmarking has resulted in quality improvement projects that have significantly improved the health outcomes of people with CF. Furthermore, these registries enable national research studies. Like all registries, barriers such as gaining ethical consent across multiple jurisdictions need to be streamlined as well as overcoming IT barriers through the development of user-friendly interfaces and ensuring that databases are relational and linked. The harmonization of data in international registries will allow international comparisons and collaborative research opportunities that will benefit our patients.

Plenary 19
THE AUSTRALIAN CONTRIBUTION TO THE EU FRAMEWORK 7 PROJECT RD-CONNECT: REGISTRIES, BIOBANKS AND CLINICAL BIOINFORMATICS

Matthew Bellgard[1,2]

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RD-Connect is a global infrastructure initiative linking up databases, registries, biobanks and clinical bioinformatics data used in rare disease for researchers worldwide. RD-Connect is a 6-year initiative, funded through the European Union, connecting researchers across the world, with the aim of developing an integrated research platform in which complete clinical profiles are combined with omics data and sample availability for rare disease research; in particular, research funded under the International Rare Diseases Research Consortium (IRDiRC). In this talk, I will provide an overview of the work undertaken by the Australian consortium for the EU RD Connect project, funded through the NH&MRC. This work spans patient registries, phenotypying, linking biobanks, a bioinformatics workflow to enable integrative omics analysis, as well as 3D facial analysis.

Plenary 20
DISEASE REGISTRIES AND THE HUMAN VARIOME

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Convergence of the contributions of engineers, mathematicians, ethicists, lawyers, informaticians, scientists and medical researchers with the community stakeholders will help to frame the research questions and find the answers. Registries are a significant resource to facilitate research and provide options for participation. An example of this is the registry for hereditary hemorrhagic telangiectasia (HHT), where health and clinical information from patients diagnosed with HHT are provided by participants to create economies of scale. This platform enables consideration of the needs of the HHT population, and facilitates international clinical trials. Multiple high penetrance gene mutations in adult onset genetic disorders have proven clinical validity and utility. The identification of mutations in disease causing or predisposing genes may be used in a preventive role, where at-risk unaffected family members can be tested for a pathogenic family specific mutation, thus personalising risk assessment and risk management. Accurate assignment of pathogenicity of variants is essential for clinical use. International collaborations such as The Human Variome Project and the Global Alliance for Genomic Health, in conjunction with substantial international databases, LOVD and Clinvar, have created the platform for sharing on a global scale and thus determination of genetic variation across many disease related genes and most populations. In the Australian context, where the population is increasingly heterogeneous, this knowledge will serve to realize the

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full potential of genomics in enhancing healthcare services for our communities.

Plenary 21
HUMAN VARIOME PROJECT — AUSTRALIA — ROAD MAP TO 2020

Vincent Harley

Human Variome Project Australian node (HVPA) Hudson Institute of Medical Research, Melbourne, VIC, Australia

Rates of variant annotation are falling well behind rates of variant discovery. Some 85% of variants are rare with no listed effect and limited validation. For the phenotype observed in an individual, there is often insufficient evidence for association with the variants found. Sharing of variants from unsolved cases is therefore an essential endeavor. With NGS moving into a service setting, most human genetic variants will be detected in a diagnostic context. Genetic variants will become part of a patient's medical record, and annotating variation in the human genome gives hope for complex disorders, cancer predispositions, and so on. The HVP goal is to increase information about clinically validated and classified genomic variants available in open curated databases, through effective partnering and data sharing globally. HVP has over 1,200 consortium members and 60 data provider members. The aim of the HVP-A is to capture human genome variant data from Australian clinical genetics diagnostics laboratories primarily and researchers. HVPA provides a national data sharing facility for improving clinical genetic testing services and supporting medical research. Data that has been recorded in a pathology report is submitted by diagnostic laboratories via software provided by HVPA. This allows users to check whether the same variants or patients with related phenotypes have been seen previously by other laboratories. HVPA seeks to build capacity. Variant annotation and interpretation continues to be a challenge; examples from the NHMRC program on Disorders of Sex development will be given. Established linkages to existing resources such as ClinVar and LOVD will be discussed.

Concurrent Session 1: Australasian Society of Genetic Counsellors

ASGC Oral 1
REFLECTIONS ON THE INTRODUCTION OF A GENETIC STEWARDSHIP GATEKEEPING PROGRAM

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While genetic tests are not new, their complexity has grown over the past decade with the advent of technologies such as NGS and WGS. This has opened up genetic testing to a wide range of disciplines within the hospital as clinicians from non-genetic fields wish to use genetic testing to diagnose and manage their patients. With the significant and increasing cost implications of specialized genetic testing, it has proven necessary to implement some fiscal responsibility within the Northern Sydney Local Health District. In this study, we describe the effectiveness of a gatekeeping process for specialised genetic testing. This process involves all overseas genetic tests and multigene panels ordered by clinicians outside the Genetics Department. The aim of the process is to provide education for clinicians and increase clinical benefit for patients. The process of overseeing the ordering of genetic tests across all disciplines within the area of health service also allows for reflection on clinical utility of each test ordered. By analyzing the referral indications and requests by clinicians, we will describe a shift in clinician knowledge reflected in their test requisitions. We also show a change in clinician behavior coming into line with NSW Health policy on prioritization of genetic testing. The audit has also allowed for the elucidation of clinical scenarios highlighting the clinical utility of this process.

ASGC Oral 2
AN EXPLORATION OF AUSTRALASIAN GENETIC COUNSELORS' ATTITUDES TOWARDS COMPASSION FATIGUE, MINDFULNESS AND GENETIC COUNSELING

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Aim: To collect information about the experiences of Australasian genetic counselors in relation to compassion fatigue and mindfulness. *Method:* An online questionnaire open to Australasian genetic counselors. The first part collected demographic information. The second part was the Professional Quality of Life Scale, Compassion Satisfaction and Fatigue Subscales — Revision IV. The final part was the Mindful Attention Awareness Scale. Both scales are validated. *Results*: 99 genetic counselors completed the survey. There was a significant positive correlation between genetic counselors having a high level of compassion satisfaction and a high level of mindfulness ($r = .40, p < .01$). There was a significant negative correlation between genetic counselors having high levels of compassion fatigue and low levels of mindfulness ($r = -.52, p < .01$). There is a significant positive correlation between genetic counselors feeling high levels of burnout and compassion fatigue ($r = .58$, $p < .01$). Individuals working in adult, prenatal and cardiac clinics have higher compassion fatigue (CF) and burnout (BO) scores than the other genetic counselors who answered the survey working in other areas of clinical genetics. (adult, CF, $p = .049$, BO, $p = .044$; prenatal, CF, $p = .01$, BO, $p < .01$; cardiac, CF, $p = .04$, BO, $p < .01$). Individuals that are currently experiencing compassion fatigue have higher compassion fatigue ($p = .03$) and burnout ($p = .01$) scores compared to those that do not. *Conclusion*: The results may have implications for the training of genetic counselors. There may also be implications for how genetic counselors work in various clinics thus helping reduce levels of compassion fatigue. Mindful awareness training may help reduce levels of compassion fatigue and burnout.

ASGC Oral 3
FOETAL SEX CHROMOSOME DETECTION DURING EARLY PREGNANCY VIA NON INVASIVE PRENATAL TESTING (NIPT)

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Sex chromosome detection via non-invasive prenatal testing (NIPT) raises a number of genetic counseling issues, including the ethics of reporting fetal sex in early pregnancy, detection of unexpected maternal mosaicism, reporting of high risk results where there is a high false positive rate and detection of mild conditions where there may be minimal clinical effect. In April 2015, Victorian Clinical Genetics Services launched percept™, an Australian-based NIPT service that reports fetal sex and sex chromosome aneuploidies (SCAs) in addition to common trisomies. An audit of the first 5,000 percept™ samples revealed that 44 of 128 (34%) high risk results involved SCAs. Of these, 28 were high risk for monosomy X, of which 5/19 (26%) were confirmed following diagnostic testing, including 2 cases of true foetal mosaicism for cell lines involving

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normal or structurally abnormal Y chromosomes. There were 14 false positive results, 2 of which were associated with confined placental mosaicism. Incidental findings of maternal 45,X mosaicism were recorded in 4 cases. Diagnostic confirmation was unavailable for 5 pregnancies. Cytogenetic confirmation rates were higher for 16 remaining SCAs with 7/9 cases diagnosed (2/3 XXX; 2/3 XXY and 3/3 XYY). The false positive XXY was confirmed as a maternal Y chromosome CNV in a female foetus. Diagnostic testing was either declined or unavailable for 7 patients. These results highlight the importance of pre- and post-test genetic counseling and have prompted the development of educational resources for health professionals and patients to help facilitate understanding of high risk NIPT results.

ASGC Oral 4
SHOULD NON-INVASIVE PRENATAL TESTING FOR SEX CHROMOSOME ANEUPLOIDIES (SCA) BE OPTIONAL? A CLINICAL AUDIT OF 5,409 MIXED-RISK PREGNANCIES

Melody Menezes[1,2], Samantha Ayres[1]

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Non-invasive prenatal testing (NIPT) technologies allow couples to screen for sex chromosome aneuploidies (SCA) from as early as 10 weeks gestation. However, detection rates associated with SCA screening remain unknown. Monash Ultrasound for Women has offered NIPT since March 2013. All women have pre-test genetic counseling where SCA screening is discussed with the use of a counseling aid developed in house. SCA screening is offered as an optional panel to all patients. The objective of this study was to analyze the uptake of SCA screening among women who had HarmonyTM NIPT and determine the performance of NIPT for SCA in our sample population. Statistical analysis was performed using descriptive statistics and chi-square analysis. Data from 5409 mixed-risk women who had NIPT between March 2013 and December 2015 was performed. 17% of women overall declined SCA screening following genetic counseling. Of those who had SCA screening, 33 received a high-risk assessment: 3/33 true positives, 10/33 false positives, 20/33 declined further testing with the view to test the fetus at birth. The false positive rate for the SCA panel was significantly higher than the false positive rates for the autosomal aneuploidies. We will present the findings of this audit in detail, and discuss our experience of offering SCA screening as optional aspect of NIPT. Given the high rate of women declining SCA screening and the low number of true positive results observed on our sample, we conclude that SCA screening should continue to be offered as an optional aspect of NIPT.

ASGC Oral 5
DEVELOPMENT OF A SHARED CLINICAL EXOME SEQUENCING CONSENT FORM ACROSS MULTIPLE ORGANISATIONS

Ivan Macciocca[1,2,3], Zornitza Stark[1,3], Damien Bruno[1,3], Jessica Taylor[4], SW White[1,3,5], TY Tan[1,3,5], GR Brett[1,2,3], Emma Creed[2,4], Elly Lynch[2], Community Advisory Group[2], Alon Januszewicz[6], Clara Gaff[2,5,7]

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Introduction: Informed consent for exome sequencing poses new challenges due to the complexity of the test and the many opportunities for data sharing post-test. As part of the Melbourne Genomics Health Alliance (www.melbournegenomics.org.au), a shared clinical exome sequencing consent form was developed for clinical services and testing laboratories embedded within the 10 partner organisations of the Alliance. *Method:* A working group of representatives from laboratory genetics, medical genetics and genetic counseling from partner organizations was convened to develop the consent form. Consensus was reached on key elements of the form, following review of literature and selected local and international clinical consent forms for exome sequencing. Early consumer input was achieved through the Melbourne Genomics Community Advisory Group. The documents were refined over 10 months and subjected to independent legal review. *Outcomes and conclusion:* The outcome was a single page consent form for singleton or trio analyses supported by a series of information sheets describing genomic sequencing and providing an explanation of the points that patients agree to in the consent form. To date, the consent form has been adopted by two Alliance laboratories and one clinical department and will be used to consent more than 500 patients from five hospitals over the next 2 years. Up-skilling of health professionals on the use of the consent form is ongoing. A collaborative approach to the development of an exome sequencing consent form is achievable, enabling a standardized approach to consent across multiple organizations, and facilitating data sharing in an ethically acceptable manner.

ASGC Oral 6
PERCEPTIONS OF AUTHENTICITY AND TRUST: INFORMATION-SEEKING ABOUT PERSONAL GENOMICS BY THE AUSTRALIAN PUBLIC

Chriselle Hickerton[1,2], Jacqueline Savard[3], Bronwyn Terrill[4], Erin Turbitt[1,2], Ainsley Newson[3], Clara Gaff[2,5], Kathleen Gray[2], Anna Middleton[6], Brenda Wilson[7], Sylvia Metcalfe[1,2]

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Background: Personal genomics provides the public with access to diverse personal genomic tests, often online. Personal genomic testing provides healthy individuals with access to their own genetic makeup for purposes that include ancestry, paternity, sporting ability and health. These tests are increasingly becoming accessible to all Australians but little is known about their perspectives. *Aim:* To explore Australians' awareness of personal genomic testing. *Methods*: Stage 1 of a multi-staged project involved seven focus groups with 56 members of the public who were allocated into three age groups: 18–25, 26–49 and ≥50 years. Three researchers coded transcripts independently and themes were generated. *Results*: Here we present themes focusing on awareness of personal genomic testing, information seeking, and trust in the companies offering these tests. Most were not familiar with the term 'personal genomic testing', but could deduce what 'personal genomics' might entail. Participants in the focus groups identified similar modes of information-seeking behavior, including online resources, talking to health professionals, or consulting friends whom they believe are knowledgeable. Their perceptions of reliable sources of information about personal genomic testing included observing repeated occurrences of same/similar information, irrespective of authenticity of source, and valuing promotion by 'celebrities/experts'. However, most were unclear how they could verify the authenticity of the information they received and/or found. *Conclusion*: Findings highlighted ways in which participants seek information regarding personal genomics, including challenges they face when seeking accurate,

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reliable and trustworthy information. This has implications for clinical practice, lifestyle choices and education if people trust misinformed sources.

Concurrent Session 2: Australasian Society for Inborn Errors of Metabolism

ASIEM Oral 1
THE USE OF TANDEM MASS SPECTROMETRY IN NEWBORN SCREENING

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Electrospray ionisation tandem mass spectrometry, which has been used in NSW since 1998, has now been incorporated in many newborn-screening programs worldwide. There have been many changes in methodology to prospectively screen newborns for inborn errors of amino acids, fatty acid oxidation and organic acidurias. However despite many attempts to harmonise its introduction, it remains the responsibility of each program to determine which disorders are screened, what sample to use, and what is acceptable performance. For each analyte tested there is sample, analytical and interpretative considerations. Sample aspects include the optimal time of collection after birth, the effect of feed status and gestational age. Analytical considerations include the instrumentation, sample preparation, establishing action limits, normal percentiles and expected results for proven positives as well as appropriate quality assurance protocols. The follow-up algorithms for diagnosis, which may include ratios of analytes or second tier testing on the initial sample as well as additional samples of urine and blood, need to optimize the performance metrics of resample rate, sensitivity, specificity and positive predictive value. Using various MSMS protocols since 1998, we have screened samples collected at 48–72 hours of age from 1.8 million babies, request further samples from 0.15%, and detect a disorder in 1:2691 babies with a sensitivity, specificity and positive predictive value which are currently 99%, 99.9% and 25% respectively. The use of tandem mass spectrometry in newborn screening is expanding to include many other disorders. The challenge remains whether disorders should be included because it is possible.

ASIEM Oral 2
THE NATURAL HISTORY OF ELEVATED TETRADECENOYL-L-CARNITINE DETECTED BY NEWBORN SCREENING IN NEW ZEALAND: IMPLICATIONS FOR VERY LONG CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY SCREENING AND TREATMENT

Callum Wilson[1], Emma Glamuzina[1,2], Bryony Ryder[1], Detlef Knoll[1], Donald Love[3], Phillip Shepherd[4], Jennifer Love[3], Peter Reed[5], Mark de Hora[2], Dianne Webster[2]
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Very long chain acyl-CoA dehydrogenase deficiency (VLCADD, OMIM #201475) has been increasingly diagnosed since the advent of expanded newborn screening (NBS). Elevated levels of tetradecenoyl-L- carnitine (C14:1) in newborn screening blood spot samples are particularly common in New Zealand; however, this has not translated into increased VLCADD clinical presentations. A high proportion of screen-positive cases in NZ are of Maori or Pacific ethnicity and positive for the c.1226C>T (p.Thr409Met) ACADVL gene variant. We performed a retrospective, blinded, case-control study of 255 cases, born between 2006 and 2013, with elevated NBS C14:1 levels between 0.9 and 2.4 μmol/L, below the NZ C14:1 notification cut-off of 2.5 μmol/L. Coded healthcare records were audited for cases and age- and ethnicity-matched controls. The clinical records of those with possible VLCADD-related symptoms were reviewed. The follow-up period was 6 months to 7 years. Two of 247 cases (0.8%) had possible VLCADD-like symptoms while four of 247 controls (2%) had VLCADD-like symptoms ($p = .81$). Maori were overrepresented (68% of the cohort vs. 15% of population). Targeted analysis of the c.1226 locus revealed the local increase in screening C14:1 levels is associated with the c.1226C>T variant (97/152 alleles tested), found predominantly in Maori and Pacific people. There was no increase in clinically significant childhood disease, irrespective of ethnicity. The study suggests that children with elevated C14:1, between 0.9-2.4 μmol/L, on NBS are at very low risk of clinically significant childhood disease. A minimally interventional approach to managing these patients is indicated, at least in the New Zealand population.

ASIEM Oral 3
ARGININE AS AN ANTI-AGGREGATION AGENT AND A POTENTIAL THERAPEUTIC FOR TREATMENT PHENYLKETONURIA ASSOCIATED WITH AGGREGATED MUTANT PAH PROTEIN

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Background: Phenylketonuria (PKU), an autosomal recessive inborn error of phenylalanine metabolism, is predominantly caused by mutations in the PAH gene, and shows marked genetic heterogeneity. A subset of these missense mutations, specifically those in the N-terminal region are known to cause aggregation of the PAH protein, hypothesised to be a result of misfolding of the mutant polypeptide. In some genetic disorders such misfolding and aggregation lead to a greater rate of targeted degradation. Arginine is a protein stabilizer, proposed to exert an anti-aggregation effect by increasing the activation energy of protein aggregation. This study aims to test whether arginine supplementation has an anti-aggregation effect and might improve expression and activity of selected PAH mutants. *Methods*: Three missense mutations at the N-terminus of the PAH polypeptide (p.Phe39Leu, p.Leu48Ser and p.Ile65Thr), known to form highly insoluble protein aggregates in the cell were expressed in a COS-7 cell line. Cells were treated with varying concentration of arginine, followed by subsequent analyses including immunofluorescence, SDS-PAGE and enzymatic assays to test for improved expression and catalytic activity. *Results*: The three missense mutations all showed high levels of punctate staining in untreated cells. We found that cells supplemented with arginine showed significant reduction in the number of aggregates in the cells. *Conclusion*: Preliminary results reveal that arginine shows beneficial anti-aggregation effect, leading us to hypothesize that it might constitute a promising therapeutic agent in specific cases of PKU. Further investigations are in progress to assess the effect of arginine on PAH protein levels and catalytic activity.

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ASIEM Oral 4
LEIGH-LIKE SYNDROME DUE TO HOMOPLASMIC M.8993T>G VARIANT WITH HYPOCITRULLINEMIA AND UNUSUAL BIOCHEMICAL FEATURES SUGGESTIVE OF MULTIPLE CARBOXYLASE DEFICIENCY (MCD)

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Background: Leigh-like syndrome is considered in individuals who do not fulfil the diagnostic criteria but have features of Leigh syndrome, a relentlessly progressive neurodegenerative disorder of early childhood. *Case:* A unique presentation of Leigh-like syndrome is described in a 2-year-old boy with elevated 3-hydroxyisovalerylcarnitine (C5-OH) on NBS. Subsequent persistent plasma elevations of C5-OH and propionylcarnitine (C3), and fluctuating urinary markers suggested MCD. Clinical features at 13 months of age comprised psychomotor delay, central hypotonia, myopathy, failure to thrive, hypocitrullinemia, recurrent decompensations with lactic acidosis and an episode of hyperammonemia. Biotin treatment was associated with increased activity levels, alertness, and attainment of new developmental milestones, despite lack of significant correlation with biochemical improvements. *Results*: Normal enzymology and mutational analysis excluded MCD. Biotin uptake studies were normal. Complex IV activity was mildly reduced in skeletal muscle. Apart from a small lactate doublet on spectroscopy, brain MRI was normal. Whole exome sequencing analysis failed to identify any other variants which could likely contribute to the observed phenotype, apart from the homoplasmic (100%) m.8993T>G variant initially detected by mtDNA sequencing. *Discussion*: Hypocitrullinemia has been reported in patients with m.8993T>G mutation and other mitochondrial disorders. Persistent elevations of C3 and C5-OH have previously only been reported in one other patient with this mutation. We suggest considering the m.8993T>G variant early in the diagnostic evaluation of MCD-like biochemical disturbances, particularly when associated with hypocitrullinemia on NBS and subsequent confirmatory tests. An oral biotin trial is also warranted.

ASIEM Oral 5
CHARACTERIZING BIOCHEMICAL EFFECTS OF COMPLEX I DEFICIENCY IN HUMAN EMBRYONIC KIDNEY 293 (HEK293T) CELLS

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Mitochondrial disorders are the most common inborn error of metabolism, affecting 1 in 5,000 live births; the most common being complex I (CI) deficiency. Deleterious mutations in CI subunits are varied in pathological presentations; NDUFS4 mutations are typically associated with progressive neurodegeneration, whereas mutations in NDUFS6 are associated with acidosis and early mortality. Current treatments are inadequate, emphasizing the need for effective and accurate experimental systems. We characterized HEK293T knockouts for NDUFS4 and NDUFS6, due to their association with disease and different severities. The ability to compare with isogenic controls increased experimental sensitivity. Cells were investigated using the Seahorse XF24-3, which can measure oxygen consumption in live cells, and by assays for mitochondrial membrane potential, ATP synthesis, and respiratory chain enzyme activity. CI activity and ATP synthesis were decreased in both knockouts to a comparable degree. The Seahorse XF24-3 and membrane potential assays showed differences in severity between the cell lines. Maximal respiration was reduced to 30% of controls in NDUFS6 knockouts (n=5, p=0.0001) and 50% in NDUFS4 knockouts (n=5, p=0.0010). Broadly, a CI defect was detected in both knockouts; however, the Seahorse XF24-3 and mitochondrial membrane potential assays were more sensitive, likely due to their measuring function in the more physiological situation of intact cells. These results are consistent with both mouse knockouts and human presentations. The data support the use of this model system to further understand mitochondrial disorders and to test novel treatments, particularly important given the paucity of effective therapies and clinical variation in these disorders.

ASIEM Oral 6
OUT OF HOURS TELEPHONE SUPPORT PREVENTS HOSPITAL PRESENTATIONS AND ADMISSIONS IN CHILDREN WITH GENETIC METABOLIC DISORDERS

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Introduction: The Genetic Metabolic Disorders Service at the Children's Hospital at Westmead provides 24- hour on-call support to 600+ patients, of who 20% are at high risk of metabolic decompensation. Service requirements have previously been neither quantified nor qualified. In determining demand, a data collection tool was developed to simplify collection. *Methods*: A database, the Metabolic Occasion of Service Electronic Record (MOOSER) was developed enabling data entry using an iOS interface. After proof of concept testing and enhancements, MOOSER was released in May 2014. To enhance usability, auto-entry of pertinent patient details was incorporated, including support for generation of overnight clinical handover. Demand data for on-call services was collected over an initial 45-day period. Entries were clinically categorized, identifying preventable hospital admissions. An analysis of a subset of out-of-hours interactions was performed. *Results*: Thirty-eight children accounted for 84 telephone interactions, totalling 700 minutes, with 15% of activity occurring between midnight and 8:30 am. Seven children were asked to present to hospital; four were admitted to wards and three were managed in short-stay/emergency department. Hospital admission was prevented in 19% of interactions, where significant clinical metabolic advice was given to change the patient- specific treatment regimen to stabilise the patient. *Conclusion*: On-call services also provide direct clinical advice to patients and families and prevent admissions. Ongoing data collection will further validate the usefulness of telephone support both during and outside of standard working hours. A cost-benefit analysis is needed to determine the monetary value of telephone support services.

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Concurrent Session 3: Australasian Society of Diagnostic Genomics

ASDG Oral 1
HIGH READ DEPTH NIPT ENABLES TRISOMY DETECTION AT LOW FETAL FRACTION WITH HIGH SENSITIVITY AND SPECIFICITY AND VERY LOW FAILURE RATE

Mark Pertile[1,2], Nicola Flowers[1], Katrina Scarff[1], Alison Archibald[1], Justine Elliott[1], Grace Shi[1], Sara Cronin[1], Ralph Oertel[1], Fiona Norris[1], David Francis[1], David Amor[1,2], Damien Bruno[1]

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Non-invasive prenatal testing (NIPT) can achieve high sensitivity and specificity with very low failure rates by analyzing cell-free DNA from maternal plasma at high sequencing read depths. To investigate this we reviewed 5,172 consecutive referrals from high- and average-risk pregnancies referred to Victorian Clinical Genetics Services and processed using percept^{TM} NIPT. Percept uses whole-genome massively parallel sequencing of cell-free DNA from maternal plasma to identify pregnancies at increased risk for autosomal trisomies (13,18,21) and sex chromosome aneuploidies. The test has been validated to detect trisomy from as little as 2.5% fetal fraction, with an observed 'no call' rate of 0.2% (10/5172). Cytogenetic outcome data were obtained in 84/85 (99%) cases with increased risk results for standard trisomies. High-risk results were confirmed in 46/46 (100%) T21, 5/5 (100%) T18 and 9/15 (60%) T13. One case of double-aneuploidy was also confirmed. Confined placental mosaicism for T13 was responsible for 2/2 false-positive results where placental material was available for analysis. Of 7 'intermediate (borderline) risk' results for all trisomies, 1/7 (14%) was confirmed with T21. Finally, 8/84 (10%) pregnancies miscarried without opportunity for cytogenetic confirmation. Overall confirmation rate for all trisomies with cytogenetic outcome data was 62/74 (84%). No known false-negative outcomes have been reported from approximately 4,000 births. These data provide evidence for the clinical utility of high read depth NIPT utilizing normalized chromosome values (NCV), which places low emphasis on the requirement for fetal fraction above 4%. Further evidence is provided in support of this claim.

ASDG Oral 2
NONINVASIVE PRENATAL TESTING (NIPT) FOR SCREENING PREGNANCIES OF BALANCED RECIPROCAL TRANSLOCATION CARRIERS

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Background: Carriers of balanced reciprocal translocations are at increased risk of producing embryos that carry an unbalanced form of the parental rearrangement. Current testing available to translocation carrier couples includes Pre-implantation Genetic Diagnosis (PGD) or invasive testing using CVS or amniocentesis. A new approach is to use whole genome sequencing data obtained from NIPT to screen for segmental copy number imbalances associated with the translocation. *Aim:* We sought to investigate the utility of NIPT to screen pregnancies of balanced reciprocal translocation carriers and to determine guidelines for the screening of pregnancies by NIPT in our laboratory where we offer percept^{TM}.*Methods*: Normalized chromosome coverage data were examined in 11 cases referred for NIPT and translocation screening. Cases underwent additional assessment for segmental imbalances using WISECONDOR(1) and Cartagenia OneSight Software(2).

Results: To date, 11 pregnancies have been screened for chromosomal imbalances associated with the known carriers of balanced reciprocal translocations. Of these, 4 showed an abnormal NIPT result that was confirmed in the fetus by invasive testing. Segmental chromosomal imbalances ranged in size from 10–67 Mb. Invasive testing in 3 pregnancies with normal results confirmed the normal/balanced NIPT results obtained. The remaining 4 pregnancies with normal NIPT results are ongoing. *Discussion*: These data demonstrate the clinical utility of NIPT for screening pregnancies of reciprocal translocation carriers. In translocations meeting the determined guidelines (size of translocated segments, ascertainment, gestation), NIPT can offer another option for these couples, at high sensitivity.

ASDG Oral 3
ACCREDITING AUSTRALASIA'S FIRST CLINICAL WHOLE GENOME SEQUENCING (WGS) SERVICE

Aga Borcz[1,2], Michael Buckley[1,2,3], Peter Budd[1,2], Leslie Burnett[1,2,3,4], Liviu Constantinescu[1,2], Joe Copty[1,2], Mark Cowley[1,2], Marcel Dinger[1,2], Lisa Ewans[1,2,5], Maria Gonzalez[1,2], Tudor Groza[1,2], Warren Kaplan[1,2], Maria Lubka-Pathak[1,2], Ben Lundie[1,2], John Mattick[1], Scott Mead[1,2,3,5], David Miller[6], Paula Morris[1,2], Mark Pinese[1,2], Tony Roscioli[1,2,5], Dahlia Saroufim[1,2], Aaron Statham[1,2], Justin Stockmyer[1,2], Kevin Ying[1,2]

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Background: Garvan's KCCG operates the Illumina HiSeq X Ten whole genome sequencing (WGS) system. This enables a minimum 30x coverage of the human genome. Application of WGS to clinical practice requires accreditation. Worldwide, very few WGS facilities have gained accreditation and, to our knowledge, none have achieved the international standard of ISO 15189. Aims: To describe the process for NATA/RCPA accreditation for human clinical WGS, including certification to ISO 15189. *Methods*: Following WGS facility commissioning, a 12-month plan progressively upgraded infrastructure and processes to accreditation requirements. Key accreditation developments included a Quality Management System to control procedures and documents, introducing audit and corrective action programs and a clinical Code of Conduct for all staff. Innovations included wikis and job ticketing systems facilitating rapid communication between expert teams. WGS-specific issues included design and execution of validation plans to meet NPAAC Requirements for in-house IVDs and RCPA Guidelines for massively parallel sequencing; online web requesting; information systems capable of integrating phenotype ontologies with genotypes; informatics meeting NPAAC Requirements for information communication; optimisation of filtering pipelines; and structured clinical reports compliant with ACMG Guidelines. *Results*: NATA accreditation was achieved at first submission. *Discussion*: The initial WGS IVD detects SNVs and indels <20nt in bioinformatically defined panels. While it can diagnose individuals, it is optimized for familial trios. Although our IVD outperformed Sanger sequencing during validation, we will routinely orthogonally confirm medically significant findings in the short term. The second version of our WGS IVD will include CNV detection at resolutions comparable to current microarray technologies.

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ASDG Oral 4
NEXT GENERATION SCREENING: TRUSIGHT ONE 'CLINICAL EXOME' FOR PRECONCEPTION SCREENING IN CONSANGUINEOUS COUPLES

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Background: Autosomal recessive (AR) disorders are a major cause of morbidity and mortality. Consanguineous couples are at increased risk for having a child with these disorders but to date, risk assessment based on family history and/or ethnicity often added little to that based on empiric observational data. Therefore, exome (and in the future, whole genome) sequencing offers the prospect of 'the screen for everything', providing information that can inform reproductive choice in this at-risk group. More broadly, it may provide a paradigm for assessment of the practicability and effectiveness of this screening approach in the general population. *Study design:* We used the TruSight One 'clinical exome', which includes 4,813 genes linked to human disease, to pilot screen 15 consanguineous couples who were planning a pregnancy for AR and X-linked disorders. *Results*: Three couples were found to be at risk of having children affected by AR disorders: severe neurological conditions ($n = 2$), and a metabolic disorder which is relatively straightforward to treat but can be difficult to diagnose and can have severe consequences for an untreated child ($n = 1$). Interviews conducted with the couples pre-test identified an intention to utilize any positive findings in their future pregnancy planning. *Conclusion*: Variant interpretation remains a considerable challenge, which will limit the sensitivity of this approach. Nonetheless, our results indicate that the benefits of screening are likely to be considerable and a major advance over a targeted approach.

ASDG Oral 5
GENOMIC APPROACHES AND NEW DIAGNOSES IN OCULAR ANTERIOR SEGMENT DISORDERS

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Introduction: Disorders of the ocular anterior segment, such as Axenfeld-Rieger syndrome, Peters anomaly and sclerocornea, occur due to abnormalities in several developmental pathways in eye embryogenesis contributing to their marked clinical and genetic heterogeneity. We seek to determine the utility of genomic approaches to genetic diagnosis in these conditions. *Methods*: We performed NGS in 29 probands with ocular anterior segment abnormalities, where copy number variants were excluded by CGH microarray. A panel targeted at over 4,000 known disease genes was used in 10 patients (Illumina TruSight One, HiSeq 2500), while whole exome sequencing was used in the remaining 19 (Agilent SureSelect, Illumina HiSeq 4000).We examined known anterior segment abnormality genes, syndromic and non-syndromic, and genes contributing to overlapping genetic eye disorders such as cataracts and microphthalmia. A customized alignment and variant calling pipeline was utilized, and variants of interest were confirmed with Sanger sequencing and segregation studies. *Results*: In our cohort of 29, likely causative mutations were found in 41% (12/29) of patients. Mutations were found in the known anterior segment abnormality genes FOXC1/PITX2 in 4/29 patients, and also in the more rarely reported genes COL4A1 and PXDN. Novel phenotypes were found associated with the anophthalmia gene SOX2, and in two patients with GJA8 mutations. Mutations were also found in the syndromal gene ADAMTS17. *Discussion*: This study demonstrates a significant yield of mutations in a cohort of patients with ocular anterior segment abnormalities, providing new diagnostic and management information in all cases.

ASDG Oral 6
A PANEL APPROACH USING MASSIVELY PARALLEL SEQUENCING TO DIAGNOSE GENETIC LEUKODYSTROPHIES: FIRST RESULTS FROM THE CHW LABORATORY

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Background: There are many molecular causes for a clinical diagnosis of leukodystrophy. Genetic testing for individual genes may be a time consuming and expensive process, hence designing a panel using massively parallel sequencing to analyze multiple genes concurrently is an attractive approach. Aim: To present the first six patients tested using a multi-gene panel approach. *Methods:* Six adult patients with undiagnosed leukodystrophy were consented. These patients had already undergone multiple unrevealing investigations prior to utilising the leukodystrophy panel. Massively parallel sequencing using the Trusight One clinical exome was performed, and the sequences of 79 genes known to cause leukodystrophy analyzed. *Results*: Disease causing mutations were found in 3 out of 6 patients, with the following diagnoses being made: CARASIL, 4H syndrome, and progressive leukoencephalopoathy with ovarian failure. One patient had pseudo-deficiency variants for metachromatic leukodystrophy confirmed (previously known). The remaining two patients did not have pathogenic variants detected. *Discussion/Conclusion*: The leukodystrophy panel was successful in making a diagnosis in 50% of patients in this initial cohort of adult patients.

Concurrent Session 4: Australasian Association of Clinical Geneticists

AACG Oral 1
THE CLINICAL UTILITY OF WHOLE EXOME SEQUENCING IN A DIVERSE NEW ZEALAND COHORT OF CLINICAL CONUNDRUMS

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Aim: To determine the clinical utility of whole exome sequencing (WES) for a series of patients referred to Genetic Health Service New Zealand. *Method:* WES using a trio design was performed on 42 individuals from 12 families. All probands had prior expert clinical review and appropriate investigations yet a molecular diagnosis remained elusive. Clinical diagnoses included

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multiple congenital anomalies (4), developmental delay (4), myopathy (1), pancreatic failure (1), cardiomyopathy (1) and skeletal dysplasia (1). Exome sequencing was provided by NZGL with Nextera 37Mb exome capture and paired-end sequencing on an Illumina platform. Data were processed for alignment, variants called according to the current best practice guidelines using the GATK (Broad Institute) and candidates validated using Sanger sequencing. *Results*: A likely or definite molecular diagnosis was made in 7/12 families, an overall diagnostic yield of 58%. Seven families had a child with a presumed sporadic condition, four had sibling recurrences and one had an X-linked inheritance pattern. The highest diagnostic yield was in those with sibling recurrences, with 4/4 solved. Of the seven diagnoses made, four were previously recognized pathogenic mutations, one was a novel mutation in a known gene and two were in genes yet to be associated with a human disease phenotype. *Conclusion*: WES using a trio design was a useful tool to obtain a molecular diagnosis in this cohort of patients, particularly for families with sibling recurrence. The high diagnostic yield is likely attributable to the distinctive phenotypes studied and the depth of work-up undertaken prior to WES.

AACG Oral 2
IMPACT OF EXOME SEQUENCING ON THE DIAGNOSTIC TRAJECTORY AND HEALTHCARE COSTS OF OLDER SEQUENCING-NAÏVE CHILDREN WITH SUSPECTED MONOGENIC CONDITIONS

Tiong Yang Tan[1], Oliver Dillon[3], Zornitza Stark[1,2], Belinda Chong[1,2], Dean Phelan[1,2], Gemma Brett[1,2], Emma Creed[1,2], Patrick Yap[1,2], Maie Walsh[1,2], Lilian Downie[1,2], David Amor[1,2,3], Ravi Savarirayan[1,2,3], George McGillivray[1,2], Alison Yeung[1,2], Heidi Peters[2,4], Susan Robertson[4], Aaron Robinson[4], Ivan Macciocca[1,2], Simon Sadedin[2], Katrina Bell[2], Alicia Oshlack[2,3], Natalie Thorne[5], Deborah Schofield[2,6,7], Khurshid Alam[2,3,6], Clara Gaff[3,5,8], Susan White[1,2,3]

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Background: Exome sequencing has been shown to have diagnostic and clinical utility in different disease subgroups, including our previous study involving infants with monogenic disorders. Most published cohorts recruited children at the end of their diagnostic trajectory, having had prior sequencing. *Objective:* We sought to investigate the impact of exome sequencing in sequencing-naïve children suspected of having a monogenic disorder and evaluate hypothetical changes in their diagnostic trajectory and healthcare costs had exome sequencing been available at an earlier age. *Methods*: Children aged >2 years suspected of having a monogenic disorder were prospectively recruited from outpatient clinics of The Royal Children's Hospital and Victorian Clinical Genetics Services. All children had non-diagnostic microarrays and no prior single-gene or panel sequencing. We undertook exome sequencing with targeted phenotype-driven analysis and examined the clinical utility of a molecular diagnosis. We also evaluated hypothetical diagnostic trajectories depending on timing of exome sequencing to determine the impact on healthcare costs. *Results*: We recruited 42 children aged from 2 years 11 months to 18 years and achieved a diagnosis in 19 (45%) by exome sequencing. The average duration of diagnostic trajectory was 6 years, with each child having an average of 19 tests for diagnostic purposes, 4 clinical genetics and 4 non-genetics specialist consultations. We report health economic analyses of exome sequencing offered at the start of the diagnostic trajectory versus standard care. *Conclusion*: Exome sequencing in outpatient children with suspected monogenic conditions is clinically indicated and should be offered at the start of their diagnostic trajectory.

AACG Oral 3
MOLECULAR DIAGNOSIS OF GENETIC MUSCLE DISORDERS IN NEW ZEALAND

Gemma Poke[1], Miriam Rodrigues[2], Richard Roxburgh[3], Susannah Bawden[1], Stephanie Oates[1], Katrina Rufino[4], Kimberley Flintoff[4], Don Love[5], Elsa Parker[6], Alice Theadom[7]

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The MD-Prev study is a national population-based study that is working to determine prevalence of inherited muscle disorders in New Zealand. The study's census date was 1 April 2015, with approximately 900 affected individuals ascertained to date. Early study findings will be presented, with a focus on the individuals who have had their diagnosis confirmed molecularly. The proportion of individuals with a molecular diagnosis varies according to several factors, the main one being subtype of muscle disorder. The advantages and limitations of molecular genetic testing for muscle disorders will be discussed, with specific case examples. Special subgroups will also be discussed, such as individuals who have had a diagnosis made pre-symptomatically or prenatally.

AACG Oral 4
INHERITED PERIPHERAL NEUROPATHY: GENE PANEL OR WHOLE EXOME?

Maie Walsh[1], Katrina Bell[1], Belinda Chong[1], Gemma Brett[1], Emma Creed[2], Kate Pope[1], Jessica Taylor[2], Adrienne Sexton[2], Natalie P. Thorne[1,3,4], Alicia Oshlack[1,3], Simon Sadedin[1], Peter Georgeson[3], Eppie M. Yu[5], Timothy Day[2], Lynette Kiers[2], Michael Fahey[2,6], Elsdon Storey[2,6], Ivan Macciocca[1], Clara Gaff[3,4], Paul A. James[2], Zornitza Stark[1], Monique Ryan[1,3,5]

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Purpose: To compare the diagnostic yield of a virtual gene panel and of whole exome sequencing (WES) in patients with presumed genetic peripheral neuropathy. *Methods*: Singleton WES was performed in a cohort of patients recruited though the Royal Children's and Royal Melbourne hospitals between February 2014 and August 2015. Initial analysis was restricted to an evidence-based gene list of 55 genes associated with peripheral neuropathies and related disorders. Patients with uninformative results underwent analysis of the remainder of the WES data. *Results*: 50 patients with chronic peripheral neuropathy were recruited (age range 3–70 years, average 30 years). Of these, 11 had additional features suggestive of a complex phenotype. 12 out of 50 patients received a molecular diagnosis through the initial targeted analysis of 55 neuropathy genes (24%). A further 9 patients received a diagnosis following the analysis of untargeted exome data, increasing the overall diagnostic yield to 42%. The additional diagnoses were due to mutations in genes newly associated with neuropathies, or genes that cause complex phenotypes that have neuropathy as a feature. Another two patients received a diagnosis through SNP microarray identifying pathogenic copy number variants. *Conclusions:* This study provides evidence that WES is superior to a targeted gene panel in patients presenting with a presumed genetic peripheral neuropathy. It also outlines an approach to the reanalysis of data from patients in whom a diagnosis is not reached following initial analysis, and reinforces the importance of microarray as a first-tier test in this cohort of patients.

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AACG Oral 5
IDENTIFICATION AND ANALYSIS OF TWO NOVEL ENHANCERS OF HUMAN SOX9: IMPLICATIONS FOR DISORDERS OF SEX DEVELOPMENT

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Disorders of Sex Development (DSDs) encompass a wide spectrum of conditions and often manifest with atypical gonads or genitalia. The cause is often a flaw in the network of gene regulation responsible for development of testes or ovaries. The majority of DSD patients cannot be given an accurate diagnosis, which severely compromizes their clinical management. While mutations in coding regions of gonad genes have been important in understanding the etiology of DSD, little attention has focused on the regulatory regions of gonad genes. Recent reports of 46,XX testicular DSD patients with duplications and 46,XY gonadal dysgenesis patients carrying deletions ~500-600kb upstream of SOX9 suggest the presence of a gonad enhancer of SOX9. Using a comprehensive tiling luciferase approach, we identified two novel putative enhancers within this region. The enhancer showing the strongest activity in vitro was further analyzed and used to generate transgenic reporter mice. We show that this enhancer mediates SOX9 auto-regulation in vitro and leads to strong reporter gene expression in embryonic gonads at the time of sex determination and gonad differentiation. Our results strongly suggest that deletions or duplications (CNVs) of this enhancer lead to DSD. While this enhancer appears to be responsible for the maintenance of SOX9 expression, we have identified an additional enhancer close to human SOX9, which may be responsible for SRY-dependent up-regulation of SOX9 and subsequent testis development.

AACG Oral 6
SUCCESSES AND CHALLENGES IN THE CARDIAC GENETICS CLINIC

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Background: Over recent years, there has been a significant increase in referrals to cardiac genetics clinics with an increase in the availability of genetic testing. *Results*: As of February 2016, 814 patients had undergone diagnostic genetic testing and 208 predictive testing in the Queensland Cardiac Genetics clinic. *Discussion*: In some areas, such as sudden unexpected death in the young, this has enabled family members to not only have a diagnosis but to also be able to access genetic testing. Over time, it has become clear that cardiac genetics is a complex area of clinical genetics as there can be great inter- and intra-familial variability in clinical presentation. In addition, the increased use of large gene panels has demonstrated that mutations in particular genes can cause different cardiac conditions in different families or apparent mutations are found in genes that do not match the phenotype. Interpretation of genetic variants is also complex. A number of these clinical examples will be presented to illustrate these challenges.

Concurrent Session 5: Australasian Society of Genetic Counsellors

ASGC Oral 7
BROADENING THE DEFINITION OF GENETIC COUNSELOR ROLES

Gemma Brett[1,2], Ella Wilkins[1], Justine Elliott[1], Alison Archibald[1,2], Chloe Hanna[3], Natalie McLean[2,4], Kate Pope[1,2], Ivan Macciocca[1]
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As the genetic counseling profession continues to evolve in Australasia, it is important to recognise existing and emerging roles. The unique skill set and perspective of genetic counselors is becoming acknowledged as an invaluable asset in a variety of settings. This presentation describes and compares genetic counselor roles across the Melbourne Children's Campus, both within the clinical genetics service and other departments. These roles involve varying degrees of 'traditional' genetic counseling, with genetic counseling skills also applied to multidisciplinary clinic development and maintenance, laboratory liaison, program development and evaluation, research, education, coordination of care across multiple hospitals, support services and development of consumer and professional information resources. For example, while genetic counselors have worked in clinic coordination roles within clinical genetics services for many years, an expansion of genetic counselor roles in recent years has occurred as individual hospital departments establish designated clinics for genetic conditions. These clinics increasingly employ genetic counselors to provide clinic coordination and case management, in place of nurse coordinators. Additionally, genetic counselors are increasingly involved in facilitating the implementation of new genetic and genomic technologies. Such roles involve working collaboratively with clinical and laboratory teams to facilitate appropriate implementation of the technologies. The expertise of genetic counselors in genetics knowledge and communicating complex concepts in lay language are fundamental to their value in these roles and many others. As genetic counselors apply their skills to increasingly varied roles, it is important the emerging roles are recognised as valuable applications of genetic counseling training.

ASGC Oral 8
THE MOVE INTO PRIVATE PRACTICE FOR GENETIC COUNSELORS

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A small but increasing number of genetic counselors in Australasia are moving into private practice. This qualitative research study aims to understand the scope of the role of genetic counselors who are working in private practice and to identify ways in which these genetic counselors can be supported. In the first phase of the project, content analysis was performed on documents produced from the meetings of a private practice working party established in 2015 by the Australasian Society of Genetic Counselors (ASGC). The aim of this working party was to develop a professional guideline for genetic counseling in the private practice setting. Themes identified within the working party documents included: demand for services, business considerations, professional development

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requirements, role promotion considerations, unique professional issues and support systems desired. These themes and their subcategories informed the interview schedule used in the second phase of the project. They also formed the coding frame used to analyze interview data. In phase two, semi-structured interviews were conducted to explore the experiences of genetic counselors who have worked in private practice. Study participants were recruited from the ASGC private practice working party and the ASGC general membership. Early results from interview data will be presented. This research study will offer recommendations for training, certification and workplace. The findings can contribute to the ongoing evolution of the genetic counseling profession and the scope of practice for genetics counselors in Australasia.

ASGC Oral 9
PROVIDING OPTIONS TO CLIENTS ABOUT HOW THEY RECEIVE PREDICTIVE GENETIC TEST RESULTS: A CHANGE IN PRACTICE

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In September 2014, the Adult Genetics Unit (South Australian Clinical Genetics Service) began offering most clients the option to receive their predictive genetic test result by letter, telephone or appointment. Prior to this, results were routinely given at an appointment. This change in practice was made in an effort to promote flexibility and client autonomy. We audited 305 files from clients seen for predictive testing for a range of conditions (predominantly cancer, cardiac and neurological disorders) by six genetic counselors in the year 2015. Counselors felt comfortable allowing the majority of clients (287 / 94%) a choice: 158 (55%) chose to receive their result by letter, 113 (39%) chose telephone, and only 16 (6%) chose appointment; 18 (6%) were not given a choice and had an appointment made for them. The 112 clients who received an abnormal result by letter or telephone were given the opportunity to have a second appointment and only 16 (14%) accepted. Informal counselor interviews highlighted overall satisfaction with the new process. Counselors noted a positive effect on their workload. A preference emerged for sending results by letter due to difficulties associated with 'chasing' people by telephone and phoning at inappropriate times. Our experience supports offering clients a choice for how they receive their predictive test result. We intend to continue this process and may refine some aspects based on counselor feedback. We also intend to seek feedback from clients about this process in the future.

ASGC Oral 10
USING GENEALOGY IN CASCADE TESTING — THE VALUE IN CONCATENATION

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The breast and ovarian cancer predisposition genes, BRCA1 and BRCA2, have a low rate of new mutations and there is a high chance that two individuals that carry an identical mutation share a common ancestor at some time in the past. The Tasmanian Clinical Genetics Service has investigated the frequency of recurrently identified BRCA1/2 mutations in Tasmanians undergoing clinical testing. Out of the 52 mutations identified to date, 11 mutations have been detected between 2 and 5 times. Identifying the same mutation provides an opportunity to concatenate (link) previously independent pedigrees. Concatenation can significantly enlarge pedigrees, provide valuable penetrance data for a particular mutation, maximize the number of at-risk relatives to whom predictive testing can be offered, as well as identify relatives who are not at risk, all of which maximize the benefit of the initial mutation detection result. In some cases, concatenation can occur through the records of a genetic service; however, the TCGS is ideally situated to make use of external genealogical records to concatenate branches of distantly related pedigrees where the same mutation has been identified. To date, three extended pedigrees have been created through genealogical concatenation of seven families. The average number of predictive tests in these seven families is 21.1 and in all other BRCA1/2 families it is 6.4. Genealogical concatenation requires significant resources and currently cannot be applied routinely, but given the benefits we have been exploring novel opportunities for expanding this work including a process for engaging the expertise of volunteer genealogists.

ASGC Oral 11
BREAST CANCER GENETIC TESTING AT AUSTIN HEALTH – A CLINICAL AUDIT OF CLINICAL INDICATIONS FOR TESTING AND OUTCOMES

Megan Cotter[1], Elly Lynch[1], Anna Leaver[1], Stephanie Kearton[1], Giulia Valente[1], Mathew Wallis[1], Martin Delatycki[1,2]

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Background: Genetic testing of BRCA1 and BRCA2 is currently recommended for individuals with a greater than 10% chance of identifying a mutation as determined by the genetic testing algorithm BRCAPro1 and more recently BOADICEA2; however, the mutation detection rates for other indications for testing are not known. These include triple negative breast cancer <50 years, high grade, non-mucinous ovarian cancer <70 years, breast cancer diagnosed <35 years, and male breast cancer diagnosed at any age. *Aim:* A review of all breast cancer mutation detection testing performed by Austin Health Clinical Genetics between January 2009 and June 2015 was conducted to determine the clinical utility of current testing criteria. *Results*: In total, 667 individuals underwent testing of the BRCA1 and BRCA2 genes. Of these, 13.6% ($n = 91$) had a pathogenic mutation identified, 86.4% ($n = 576$) had an inconclusive result (variant of unknown significance or no mutation). Of all individuals tested, 27.6% ($n = 184$) did not meet any clinical criteria for testing. Of those with a known mutation, 33% ($n = 30$) had a BRCAPro score of <10%. Of those who met each clinical indication for testing, >10% had a pathogenic mutation identified. Among individuals who were offered testing on the basis of a clinical decision but did not meet any of the testing criteria, a mutation was detected in <10%. *Conclusion*: Testing for BRCA1 and BRCA2 mutations based on testing criteria is justified by >10% of individuals having a mutation in each of the categories. There appears little justification for testing outside the criteria.

ASGC Oral 12
YOUNG AUSTRALIAN WOMEN'S DECISION-MAKING ABOUT MANAGING BREAST AND OVARIAN CANCER RISK DUE TO A BRCA1/2 MUTATION

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Background: Young women aged 18–40 years with a BRCA1/2 mutation may experience their young adulthood, a formative

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developmental life stage, interwoven with an awareness of a significantly increased cancer risk. Psychosocial support needs may arise due to the tension between choosing which cancer risk management strategies to engage and when, and fundamental life events such as childbearing. This study explores how young Australian women with a BRCA1/2 mutation balance engagement with risk management strategies and young adulthood. *Method:* A grounded theory approach has been undertaken using qualitative, semi-structured interviews. The inclusion criteria included women who have a BRCA1/2 mutation, aged 18–40 years, who received their genetic test result more than 12 months prior. Data were analyzed iteratively and inductively to identify themes, ideas, concepts and categories. *Results*: Forty semi-structured interviews were conducted. Participants' decision-making about how they managed their breast cancer risk was often informed by childbearing plans and/or the presence of children. Most participants chose annual breast screening after receiving their BRCA1/2 result but many were considering a bilateral prophylactic mastectomy (BPM) once they had completed childbearing. Nevertheless, attitudes towards, and perceptions of, BPM were variable. Participants who negatively perceived BPM described feeling a 'physical revulsion' to the removal of their breast tissue. However, participants were uniform in their acceptance of having a bilateral salpingo-oophorectomy once childbearing was complete. *Discussion/ Conclusion:* These findings illustrate the psychosocial challenges young women with a BRCA1/2 mutation experience managing their cancer risk and balancing risk management strategies with childbearing.

Concurrent Session 6: Australasian Society for Inborn Errors of Metabolism

ASIEM Oral 7
PROPIONIC ACIDEMIA AFTER THE NEWBORN SCREENING

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Propionic acidemia (PA) is a rare and severe inborn error of metabolism of branched chain amino acid degradation. Patient outcome in the past 20 years included early death in 25% of the patients, frequent growth-, developmental and speech delay. The long-term prognosis was complicated by the development of secondary mitochondrial dysfunction, myopathy and basal ganglia disease. The implementation of newborn screening has had a major impact in the occurrence of clinical symptoms and in the natural course of patients with PA. More and more children with PA are able to survive to adulthood. Still, most patients detected by newborn screening prior to the development of any metabolic disarrangement, and with the best possible treatment, seem to carry a risk for developing long term sequalae. We will evaluate the different metabolic factors playing a role in the development of features like cardiomyopathy, pancreatitis or muscle disease. We will discuss recent studies which suggest a novel approach for dietary treatment and new options in pharmacotherapy. The role of liver transplantation will be also discussed. We will also focus on the psychological outcome, behavioral anomalies and autism in propionic acidemia and make suggestions to optimize long term outcome.

ASIEM Oral 8
AN INFANT PRESENTING WITH LIFE-THREATENING ACUTE METABOLIC DECOMPENSATIONS WITH HYPOGLYCAEMIA, MARKED LACTIC ACIDOSIS AND HYPERAMMONAEMIA DUE TO TANGO2 DEFICIENCY

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A female infant was the third child of non-consanguineous parents. She has had six acute metabolic decompensations requiring retrieval to the pediatric intensive care unit. Episodes are triggered by vomiting and start with hypoglycemia and then progress to severe acidosis (pH <7.0), lactic acidosis (up to16 mmol/L), hyperammonemia (up to 850umol/L) and coagulopathy with the first at 3.5 months of age. She required ventilatory support with recovery being dependent on re-establishing normal feeds. Her highest CK was 248 U/l. Urine organic acids showed marked ketoacidosis, dicarboxylic acids and lactate. In contrast, acylcarnitines showed a pattern suggestive of VLCAD deficiency. Transferrin isoforms were normal but she had a mildly elevated aglyco Apo C-III with normal mono- and disialo-Apo C-III. She has been treated with a low fat diet, medium chain triglycerides and overnight feeds. Several vomiting episodes have been aborted with ondansetron avoiding hypoglycemia. Her progress is better than her older twin siblings at the same age. These twins, a boy and a girl, presented with global developmental delay at 9 months, seizures, hypoglycemia with lactic acidosis and recurrent rhabdomyolysis with CK up to 97,500 U/l. Brain MRI in both showed generalized cerebral atrophy. The female twin developed hypertrophic cardiomyopathy. The twins died at 22 and 24 months of age. A mitochondrial disorder was suspected but whole exome sequencing showed homozygous mutations in the TANGO2 gene which is expressed in the Golgi and cytoplasm. Mutations are hypothesised to cause endoplasmic reticulum and Golgi disruption and stress.

ASIEM Oral 9
INBORN ERRORS OF THE VALINE PATHWAY

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Four enzymatic steps of the valine degradation pathway have an associated inborn error of metabolism: isobutyryl-CoA dehydrogenase (IBDH), short-chain enoyl-CoA hydratase (SCEH), 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) and methylmalonic semialdehyde dehydrogenase (MMSDHD). IBD is now generally considered to be a benign condition although it may be detected incidentally during newborn screening while MMSDHD is a very rare disorder that may be associated with microcephaly and developmental delay. IBDH and MMSDHD can be detected using conventional organic acid and acyl carnitine profiling methods. Following the recent discovery of SCEH, there has been considerable interest is this new disorder and HIBCH. Both disorders cause a variable, Leigh-like phenotype and have similar metabolic abnormalities which may be overlooked with conventional screening methods. Screening techniques have been developed for these two disorders that should stream-line their diagnosis in future. The metabolic profiles in HIBCH and SCEH, combined with their contrasting phenotypes compared to other valine pathway disorders, indicate that accumulating methacrylyl-CoA is a significant cause

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of pathology. Glutathione metabolism also appears to be involved with the detoxification of this reactive intermediate. These new metabolic findings also suggest potential treatments for HIBCH and SCEH.

ASIEM Oral 10
SLC39A8 DEFICIENCY: A CONGENITAL DISORDER OF GLYCOSYLATION WITH AN ASSOCIATED MITOCHONDRIAL DISORDER

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Background: Mutations in SLC39A8 have recently been reported as the cause of a type II congenital disorder of glycosylation (CDG) in patients with intellectual disability and cerebellar atrophy. Here we report a novel SLC39A8 variant in two siblings with strong clinical, biochemical, radiological and enzymatic evidence of a mitochondrial disorder. *Patients and Methods*: Two sisters born to consanguineous Lebanese parents presented with profound developmental delay, dystonia, seizures and failure to thrive. Brain MRI of the proband revealed cerebral atrophy and bilateral basal ganglia hyperintensities. CSF lactate was elevated at 4.2 mmol/L. Complexes IV and II + III activity were low in liver, with elevated Complex I activity. Complex IV activity was borderline low in muscle and pyruvate dehydrogenase activity was reduced. Homozygosity mapping and whole genome sequencing (WGS) were performed to provide a genetic diagnosis, together with further biochemical tests. *Results*: WGS identified a novel homozygous c.338G>C (p.Cys113Ser) variant in SLC39A8, located in one of the eight regions identified by homozygosity mapping. In silico analyses predict the variant to be deleterious. SLC39A8 is absent from the MitoCarta2.0 database but encodes a manganese and zinc transporter which localises to both cell and mitochondrial membranes. Transferrin electrophoresis of patient serum revealed an isoform pattern consistent with a type II CDG defect. Blood and urine manganese levels were low. *Conclusion*: We report a novel SLC39A8 variant in siblings with profound developmental delay. In addition to symptoms previously reported in SLC39A8 deficiency, our patients had an apparently secondary mitochondrial disorder, expanding the clinical phenotype.

ASIEM Oral 11
A CASE REPORT OF IMPROVED NEUTROPHIL FUNCTION IN GLYCOGEN STORAGE DISEASE (GSD) 1B USING PROPHYLACTIC TRIMETHOPRIM/SULFAMETHOXAZOLE

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Background: Neutropenia and impaired neutrophil function are well-known features of Glycogen Storage Disease (GSD) 1b, and are responsible for significant morbidity. Multiple mechanisms for impaired neutrophil function have been demonstrated regarding impaired motility and respiratory burst. Current standard treatment of neutropenia and related infections is with antimicrobial prophylaxis, most commonly trimethoprim/sulphamethoxazole when absolute neutrophil counts decline below 0.5, and increased neutrophil count with granulocyte colony-stimulating factor (G-CSF). There are, however, significant side effects with the use of G-CSF, including but not limited to worsening splenomegaly, hypersplenism, cutaneous vasculitis, and an increased risk of myelodysplasia and acute myelogenous leukemia. Trimethoprim/sulfamethoxazole has been shown to have demonstrated immunomodulatory effects in Wegener's granulomatosis and rheumatoid arthritis. As yet, there is no routine therapy direct at improving neutrophil function in GSDIb. *Aim:* To demonstrate the improvement in neutrophil respiratory burst and wound healing with prophylactic trimethoprim/sulphamethoxazole. *Method:* Prospective intervention with trimethoprim/sulfamethoxazole and immunological monitoring in a single patient with GSDIb. *Results*: Improvement in gastrostomy wound healing upon introduction of trimethoprim/sulfamethoxazole with concomitant increase of population of active neutrophil respiratory burst from 36% to 100%. After a dose increase 2 years later, proportion increased from 51% to 83% with concomitant gingival health improvement. *Discussion/Conclusion*: In this case study, trimethoprim/sulphamethoxazole was demonstrated to improve neutrophil function and clinical gum disease and wound healing despite declining absolute neutrophil counts. We postulate that the use of trimethoprim/sulphamethoxazole routinely in GSD1b may significantly reduce the morbidity associated with neutropenia in GSD1b patients and their subsequent reliance on G-CSF.

Concurrent Session 7: Australasian Society of Diagnostic Genomics

ASDG Oral 7
A CROSS-CENTER APPROACH FOR CLINICAL EXOME VALIDATION

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Background: As massively parallel sequencing continues to become more and more established in diagnostic laboratories around the country, many labs are beginning to shift from targeted sequencing panels to whole exome sequencing. However, despite various guidelines being available on the implementation of the technology, there are neither established standards for validating the performance of the technology nor a framework for analysis and interpretation of the ensuing variant data. Here we present our approach for the validation and implementation of clinical exome sequencing; a collaborative study between the Victorian Clinical Genetics Services and the Centre for Translational Pathology at the University of Melbourne. *Methods*: A total of over one hundred Illumina Nextera whole exome data sets were generated across the two sites on three different instruments (NextSeq500, HiSeq2500 and HiSeq4000) using both Corriell gold standards and previously analyzed clinical samples. The data was extensively analyzed to establish analytical parameters of the assay. The performance characteristics of our in-house, ACMG-based variant curation scheme were established by having multiple curators at both sites independently interpret variants identified in the relevant target regions of all 116 clinical samples.

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Results and Conclusions: Using this approach to clinical exome validation we were able to establish the performance of our clinical exome assay in extensive detail, achieving >99% analytical sensitivity, specificity and reproducibility. At the same time, the implemented variant curation scheme allowed us to achieve >95% reproducibility of variant interpretation within and between the two sites.

ASDG Oral 8
EVALUATION OF AN ALTERNATIVE TESTING ALGORITHM INVOLVING CHROMOSOME MICROARRAY AND FISH IGH ANALYSIS IN MULTIPLE MYELOMA

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Background: Multiple myeloma occurs in ∼10% of adult hematological malignancies. A range of prognostic chromosome abnormalities can be found, which can include whole chromosome gains only, IGH rearrangements, chromosome 1q gain, loss of TP53, and other complex abnormalities. Our standard testing algorithm included karyotyping with FISH analysis of CD138+ plasma cells for t(11;14), loss of chromosome 13q and TP53. Karyotype abnormalities were limited (∼25%) due poor plasma cell proliferation compared to FISH abnormality rates (∼60%). Improved diagnostic yields (∼90%) have been reported using FISH; however, extensive and labour intensive analysis of multiple probe panels is required. *Aim:* Evaluate an alternative testing algorithm involving microarray and FISH for IGH rearrangements for multiple myeloma. *Method:* A prospective cross-sectional myeloma cohort was investigated by karyotype using 24-hr synchronized and 72-hr unsynchronized cultures, FISH analysis for IGH rearrangements and chromosome microarray. The CD138+ EasySep kit (STEMCELL Technologies) was used to enrich plasma cells. Chromosome microarray was performed using the ISCA design (Agilent Technologies) but analyzed at low (1.0Mb) mean resolution. Unless of known prognostic relevance, copy number abnormalities <5Mb were not reported. *Results*: Altogether, 62 patients had karyotype, FISH and chromosome microarray analysis performed. The abnormality rate for karyotyping was 15/62 (24%), compared to 24/62 (39%) for FISH and 53/62 (86%) for microarray. Combined FISH and microarray abnormality rate was 56/62 (90%). *Conclusion*: Compared to our standard testing algorithm, increased chromosome abnormalities were found in90% of myeloma patients using IGH FISH supplemented by microarray. We no longer perform karyotyping for multiple myeloma patients.

ASDG Oral 9
EXPLORING THE USE OF WHOLE GENOME SEQUENCING AS A DIAGNOSTIC APPROACH FOR MITOCHONDRIAL DISEASES

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Aim: Mitochondrial diseases are common inherited metabolic disorders with complex and heterogeneous clinical manifestations. Mitochondrial disease can be caused by mutations in both the nuclear or mitochondrial genome. Diagnosis can be challenging, time consuming and expensive and frequently involves invasive tests such as a muscle biopsy. Whole genome sequencing (WGS) promises to be a highly effective diagnostic tool in mitochondrial disease due to its ability to simultaneously sequence both the nuclear and mitochondrial genome. *Methods*: Over 250 patients with mitochondrial disease were recruited through the Neurogenetics Department at the Royal North Shore Hospital. We included both genetically diagnosed cases (positive controls) and undiagnosed cases. WGS was performed on a Hi Seq X Ten, with small variants identified using the GATK HaplotypeCaller, copy number variants using CNVnator, and structural variants using LUMPY. Using Seave, an in-house variant filtration platform, variants were filtered against the MITOMAP and Mitocarta2.0 databases, prevalence in healthy populations, functional impact, and the likely mode of inheritance. *Results*: WGS provided very high coverage across the mitochondrial genome allowing for detection of mitochondrial point mutations and small deletions. Furthermore, we were able to estimate heteroplasmy and detect very low levels of heteroplasmic variants. Nuclear mutations were also identified, including new genetic diagnoses for several cases after the identification of mutations in the MFN2, OPA1, POLG, and SPG7 genes. *Conclusion*: WGS allows for accurate detection of variants in both the nuclear and mitochondrial genomes. This single, streamlined test promises to transform the diagnosis of mitochondrial diseases.

ASDG Oral 10
COST-EFFECTIVENESS OF SINGLETON WHOLE EXOME SEQUENCING COMPARED WITH STANDARD DIAGNOSTIC CARE

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Translation of genomic sequencing technologies from research to appropriately funded clinical practice requires evidence for cost effectiveness and optimal timing of testing. We report the results of a prospective clinical study that addressed this gap by evaluating the cost effectiveness of singleton whole exome sequencing in 40 infants with suspected monogenic disorders who underwent standard diagnostic investigations in parallel. The mean duration of the diagnostic trajectory was 13 months. A molecular diagnosis was achieved in seven infants (18%) through standard diagnostic care, with a cost per successful diagnosis of AU$27,050 (95% CI: 15,366 to 68,530). By contrast, a molecular diagnosis was achieved in 25 infants (63%) using singleton WES, with a cost per diagnosis of AU$5,047. Integrating singleton WES after exhaustive standard investigation results in an incremental cost per additional diagnosis of AU$8,112 (95% CI: 5,851 to 11,967), whereas integrating WES as a first-line test results in an incremental cost per additional diagnosis of AU$2,182 (95%CI: -5,855 to 130). When used as a first-tier test in infants with suspected monogenic disorders, singleton WES not only outperforms standard diagnostic care in terms of diagnostic utility, but is also most cost-effective.

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ASDG Oral 11
WHOLE GENOME SEQUENCING AS A MOLECULAR DIAGNOSTIC METHOD FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE — OVERCOMING THE CHALLENGES OF PSEUDOGENE HOMOLOGY AND HIGH GC CONTENT

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disorder, with a prevalence of 1 in 500. ADPKD is caused by mutations in PKD1 or PKD2. Molecular diagnosis is challenging due to six pseudogenes that share 95–97% homology to PKD1 and several regions of high GC-content. *Hypothesis:* That WGS, given its avoidance of capture and amplification bias, uniform coverage and longer read-lengths, would be better able to uniquely sequence these difficult genomic areas. *Method:* DNA-libraries were made for a cohort of 29 unrelated-patients with an ADPKD phenotype. 150bp paired-end sequencing was performed using an Illumina HiSeq X sequencer. A second pilot cohort of 4 patients underwent WGS after PCR-free library-preparation. In-house bioinformatics-pipeline aligned unique reads to the reference genome. Analysis of SNPs and CNVs was targeted to PKD1 and PKD2. Long-range PCR amplification and Sanger Sequencing or MLPA was performed to confirm all disease-causing variants. Segregation analysis was performed in 34 additional patients. *Results*: Molecular diagnosis was made in 29/33 (88%) patients. Interrogation of mapping quality demonstrated unique alignment of reads over pseudogene-homologous regions. In the standard library-preparation cohort, coverage over 4/61 exons was relatively reduced and correlated with GC-content >80%. In the PCR-free cohort, coverage was uniform across all exons. Two multi-exon deletions were also identified. All disease-causing variants were identified via Sanger sequencing or MLPA without false- positives. *Conclusion*: We demonstrate that WGS can be utilised in ADPKD. The method can overcome pseudogene homology and areas of high GC-content, which has implications for other disease groups.

ASDG Oral 12
THALASSAEMIC SYNDROME RESULTING FROM CO-INHERITANCE OF HAEMOGLOBIN ALPHA (HBA) GENE MULTIPLICATIONS WITH PATHOGENIC HAEMOGLOBIN BETA (HBB) GENE VARIANTS

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We report two cases of novel HBA (hemoglobin alpha) gene multiplication co-inherited with a pathogenic HBB (hemoglobin beta) variant. Most clinically significant thalassemic syndromes arise from globin chain imbalance in either the HBA or HBB genes. The two cases presented are remarkable as the risk of a thalassemic syndrome derives from co-inheritance of variants from both the HBA loci and HBB gene. Common HBA1/2 gene deletions were detected using gap PCR. Sequence analysis of the HBA1/2 and HBB genes was performed using Sanger Sequencing with exon dosage detected by MLPA. Case 1: A male (dob 12/07/2006) with transfusion dependent beta thalassemia. Family study detected heterozygosity for HBB:c.93-21G>A in the proband and his father. No other abnormality was detected in his parents HBA1/2 or HBB genes. Alpha globin MLPA and microarray in the proband, however, detected an apparent de novo multiplication of his HBA1/2 genes, resulting in 8 rather than the normal 4 copies of his HBA genes. Case 2: A family of four presenting in the first trimester of the mother's third pregnancy. The mother was heterozygous for HBB:315+1G>A and the father for an alpha globin 3.7kB deletion (-a/). HBA MLPA detected seven HBA genes in the father (i.e., -a/aaaaaa and not a-/aa), eight in one child (aa/aaaaaa) and three in the other (-a/aa). These two cases highlight the necessity of considering HBA1/2 multiplications as the underlying cause of chain imbalance and pathology in suspected cases of beta thalassemia where only one pathogenic variant is detected in the HBB gene.

Concurrent Session 8: Australasian Association of Clinical Geneticists

AACG Oral 7
DE NOVO AND INHERITED MUTATIONS IN THE X-LINKED GENE CLCN4 ARE ASSOCIATED WITH SYNDROMIC INTELLECTUAL DISABILITY AND BEHAVIOUR AND SEIZURE DISORDERS IN MALES AND FEMALES

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Variants in CLCN4, which encodes the chloride/hydrogen ion exchanger CIC-4 prominently expressed in brain, were recently described to cause X-linked intellectual disability and epilepsy. We present detailed phenotypic information on 52 individuals from 16

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families with CLCN4 related disorder: 5 affected females and 2 affected males with a de novo variant in CLCN4 (6 individuals previously unreported) and 27 affected males, 3 affected females and 15 asymptomatic female carriers from nine families with inherited CLCN4 variants (four families previously unreported). Intellectual disability ranged from borderline to profound. Behavioral and psychiatric disorders were common in both child- and adulthood, and included autistic features, mood disorders, obsessive compulsive behaviors and hetero and autoagression. Epilepsy was common, with severity ranging from epileptic encephalopathy to well-controlled seizures. Several affected individuals showed white matter changes on cerebral neuroimaging and progressive neurological symptoms, including movement disorders and spasticity. Heterozygous females can be as severely affected as males. The variability of symptoms in females is not correlated with the X-inactivation pattern studied in their blood. The mutation spectrum includes frameshift, missense and splice site variants and one single-exon deletion. All missense variants were predicted to affect CLCN4's function based on in silico tools and either segregated with the phenotype in the family or were de novo. Pathogenicity of all previously unreported missense variants was further supported by electrophysiological studies in Xenopus levis oocytes. We compare CLCN4-related disorder to conditions related to dysfunction of other members of the CLC family.

AACG Oral 8
IDENTIFICATION OF A NOVEL AUTOSOMAL DOMINANT SLOWLY PROGRESSIVE LATE ONSET ATAXIA CO-SEGREGATING WITH A CHROMOSOME 14 DELETION/DUPLICATION

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Background: Autosomal dominant spinocerebellar ataxias are a group of disorders that present with largely adult onset ataxia with variable speed of progression, and variable associated neurological symptoms. At least 42 types with an associated chromosomal locus have been described and in a number of these, the underlying genetic basis has been identified. *Methods*: We have identified a family with at least 22 individuals affected by a relatively pure cerebellar ataxia. Onset of ataxia is generally beyond 40 years and does not limit lifespan. The disease is very slowly progressive with individuals often ambulant many years after symptom onset. MRI of brain revealed atrophy of the superior and dorsal cerebellar vermis and mild atrophy of the cerebellar hemispheres. The brain stem was normal. *Results*: Eight individuals with ataxia from the family, separated by a total of 20 meioses, have been shown to have a novel deletion/duplication of 14q32.13 using chromosomal microarray. The deletion and duplication each include four OMIM genes. None of the eight genes are known disease genes and none are obvious candidates for the phenotype. Linkage mapping within a branch of the family shows that the del/dup co- segregates with the phenotype. *Discussion*: It is most likely that one of the deleted genes is responsible for the phenotype in this family. RNA-seq and assessment of the eight genes in WES/WGS data from individuals with unsolved ataxia are underway. Microarray can occasionally identify the cause of ataxia and should be included in the work up of individuals with this presentation.

AACG Oral 9
CLINICAL AND MOLECULAR CHARACTERIZATION OF FRONTONASAL DYSPLASIA

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Objectives: (1) To clinically characterise a cohort of patients with FND to identify phenotypic subgroups. (2) To use microarray, a custom targeted craniofacial panel and whole exome sequencing to identify the molecular spectrum of mutations in known genes and novel FND genes. *Methods*: We used the databases of the Victorian Clinical Genetics Services and Royal Children's Hospital Craniofacial Clinic to identify potential participants with FND. We also recruited patients prospectively from outpatient clinics, inpatient referrals and international collaborators. We used a standardized assessment and 3-dimensional photography for clinical phenotyping. We undertook microarrays and a custom SureSelect NGS panel to screen for variants in known FND genes. Exome sequencing was used to identify novel genes in mutation-negative patients. *Results*: Our cohort of 17 probands comprises Craniofrontonasal dysplasia (6), FND (7) and Oculoauricolofrontonasal syndrome (3), as well as a 3-generational family with a novel Xq13.1 duplication involving the EFNB1 gene. We also characterized three provisionally unique FND phenotypes. We identified one novel mutation in EFNB1, and functional studies are underway to determine the clinical significance of the variant identified by exome sequencing. *Conclusions*: Our findings confirm that FND is a clinically and genetically heterogeneous group that requires detailed phenotyping in order to establish the causative molecular lesion.

AACG Oral 10
THE GENETIC CAUSES OF AICARDI SYNDROME: X MAY NOT MARK THE SPOT

Thuong Ha[1], Rosie Burgess[2], Morgan Newman[3], Melody Li[4], Alison Gardner[5], Duyen Pham[5], Raman Kumar[5], Christopher Reid[4,6], Steven Petrou[4], Nicholas Smith[5,7], Sam Berkovic[2,8], Clare van Eyk[9], Michael Lardelli[3], Ingrid Scheffer[6], Jozef Gecz[1,5], Mark Corbett[5]

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Aicardi syndrome (OMIM 304050; AIC) is a rare, almost female exclusive, severe neurodevelopmental disorder defined by chorioretinal lacunae, infantile spasms and a characteristic malformation of cortical development that includes agenesis of the corpus callosum. AIC is traditionally thought to be an X-linked male lethal

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disorder however, despite numerous investigations the causes of AIC remain largely enigmatic. This study aim to identify the genetic causes underlying AIC. We performed whole exome sequencing (WES) on eight parent-proband trios and four additional individuals diagnosed with AIC. We enriched for likely causative variants based on: predicted pathogenicity, amino acid conservation, variant allele frequency and clinical significance. In four different individuals we identified de novo variants in the ANKRD32, HCN1, SZT2 and WNT8B genes respectively. We showed, using in vitro assays that the HCN1 variant left-shifted the voltage-dependence of activation resulting in a loss of function, while the WNT8B variant had a dominant negative effect on WNT signaling; the functions of SZT2 and ANKRD32 are as yet unknown. We used morpholino knockdowns of all the genes we implicated in AIC and a recently published AIC gene (TEAD1) in zebrafish. We identified a unifying morphant phenotype of AIC-like eye and brain defects among 2/3 genes tested so far. Our study demonstrates that AIC is genetically heterogeneous and, importantly, we challenge the dogma that AIC is X-linked. We show that the WNT signalling pathway, which is already well known for its roles in eye and brain development, is a contributor to the molecular pathogenesis of AIC.

AACG Oral 11
CHILDREN DIAGNOSED WITH TUBEROUS SCLEROSIS ANTENATALLY/ BEFORE SEIZURES — ARE THEY A LESS SEVERE GROUP OF PATIENTS?

Clara Chung[1], John Lawson[1,4], Vanessa Sarkozy[1,4], Sean Kennedy[1,4], Kate Riney[2], Orli Wargon[1], Stephen Cooper[1], Antonia Shand[3], David Mowat[1,4]

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Background: Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by mutations in the TSC1 or TSC2 gene with a birth incidence of 1 in 6,000. TSC is associated with variable neurodevelopmental outcomes, seizures and benign tumours in various organs. In most cases, the diagnosis is made after seizures have occurred. Approximately 17% are diagnosed antenatally. Neurodevelopment outcome is linked to seizure severity. Trials aimed at improving outcome with early use of vigabatrin and mTOR inhibitors are underway. Early diagnosis of TSC, preferably prior to seizure onset, will be needed to maximize benefit. *Aim/Methods*: Retrospective medical records review of all TSC patients born between 2001 and 2015 who were seen in the TSC clinic at Sydney Children's Hospital. We compared those diagnosed pre- and post-seizure to determine if a pre-seizure TSC diagnosis results in better long-term neurodevelopmental outcome. *Results*: 74 patients were ascertained: 34 diagnosed pre-seizure (21 antenatally), 40 diagnosed post-seizure. (1) Of those diagnosed pre-seizure, 77% presented with cardiac rhabdomyoma(s). (2) 72% of the pre-seizure cohort developed clinical seizures — 53% by 12 months of age, compared with 87% of the post-seizure cohort. (3) 47% of the pre-seizure patients had developmental disability (DD) compared with 68% of the post- seizure patients ($p = .027$). *Conclusion*: (1) Pre-seizure TSC cases have a milder clinical course with less severe DD and fewer seizures. (2) Fetuses/children with cardiac rhabdomyomas ought to be assessed for possible diagnosis of TSC. 3. Pre-seizure TSC infants need active management to identify onset of seizures and provide early treatment.

AACG Oral 12
ANTENATAL DIAGNOSIS OF MARKED HYDROCEPHALUS (CCDC88C-RELATED) CAN HAVE A SURPRISINGLY GOOD OUTCOME

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Background: Non-syndromic congenital hydrocephalus is etiologically diverse. A genetic cause is often suspected but cannot always be confirmed. The most common genetic cause is the L1CAM-related X-linked hydrocephalus and that explains only 5–10% of all male cases. This underlines a current limitation in our understanding of the genetic burden of non-syndromic congenital hydrocephalus, especially for those cases with likely autosomal recessive inheritance. The prognosis for most cases of severe congenital hydrocephalus is poor, with a majority of surviving infants displaying significant intellectual impairment despite surgical intervention. It is for this reason that couples with a prenatal diagnosis are given the option, and may opt, for termination of the pregnancy. *Aim and Method:* We aim to review the neurodevelopmental outcomes of patients with CCDC88C-related autosomal recessive hydrocephalus by analyzing all previously reported cases and presenting two new families. *Results*: Individuals who did not require multiple surgical revisions and had a more distal truncating mutation of the CCDC88C gene had normal neurodevelopment in most cases. *Conclusion*: These reported cases suggest that children with CCDC88C-related autosomal recessive hydrocephalus can have a normal neurodevelopmental outlook despite severe hydrocephalus on antenatal and neonatal imaging studies. The likelihood of a normal outcome may be mutation-specific and/or relate to the presence of additional surgical complications. We recommend including CCDC88C analysis in cases of severe non-syndromic congenital hydrocephalus with possible recessive inheritance, especially when aqueduct stenosis with or without a medial diverticulum are seen.

Concurrent Session 9 — Submitted Orals

Oral 1
THE EVOLVING ROLE OF GENOMIC DYSMORPHOLOGY

Susan Marie White[1], Zornitza Stark[1], Maie Walsh[1], Patrick Yap[1], David Amor[1,2], Alison Yeung[1], George McGillivray[1], Ravi Savarirayan[1,2], Clara Gaff[3,4], Ivan Macciocca[1,3], A/Tiong Yang Tan[1,2]

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Next-generation sequencing is changing the practice of dysmorphology. In the Melbourne Genomics Health Alliance, we undertook a prospective study of singleton whole exome sequencing (WES) in parallel with standard care in 145 syndromic children. Results on 80 infants are complete, with a molecular diagnosis by WES reached in 47 (59%), compared with 14% by standard care. One third of diagnoses resulted in a change to the child's medical care. This presentation will reflect upon the many ways that the WES project has changed our dysmorphology practice. 80% of diagnoses

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were in genes suspected clinically, emphasizing the importance of accurate phenotyping. We were also reminded of its limits: 20% of our diagnoses were in genes thought clinically unlikely or not suspected at all. Clinical geneticists worked closely with laboratory scientists to facilitate phenotype-driven selection of variants for curation and accurate interpretation of the clinical validity of genomic data. This improved the genomic literacy within our clinical team. Dysmorphology meetings broadened scope to include discussion of patient suitability for exome testing and generation of patient-specific gene lists. We introduced multidisciplinary meetings with clinical and molecular genetics, bio-informatics and researchers to reach consensus on variant pathogenicity. We started a genomics clinic to integrate WES into clinical care and employed a genomics genetic counselor who coordinated workflow processes, laboratory liaison and case management. In addition to the benefits of improved diagnosis rates and patient outcomes, integrating genomics into our practice is revolutionizing the way we work.

Oral 2
A CLINICALLY DRIVEN VARIANT PRIORIZATION SCHEME OUTPERFORMS IN SILICO APPROACHES FOR THE DIAGNOSTIC ANALYSIS OF WES DATA

Zornitza Stark[1], Tiong Yang Tan[1,2], Natalie Thorne[1,2,3], Alicia Oshlack[1,2], Simon Sadedin[1], Melbourne Genomics Health Alliance[3], Susan M White[1,2], Paul A James[4]

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Background: Rapid identification of clinically significant variants is key to the successful application of next generation sequencing technologies in clinical practice. *Methods*: The Melbourne Genomics Health Alliance (MGHA) variant prioritization scheme employs a gene prioritization index (GPI) based on clinician-generated a priori gene lists, and a variant prioritization index (VPI) based on rarity, conservation and protein effect. We used data from 46 diagnosed patients to test the scheme's ability to rank disease-causing variants highly. The phenotypic and WES data from the same patients was used to evaluate the performance of other gene and variant prioritization tools such as Exomiser, CADD and Condel scores, PhenoTips and Phenomizer. *Results*: The average rank of disease-causing variants using the MGHA prioritization scheme was 2.48, with 51 of 58 variants (87.9%) ranked within the top 5 variants in the patient datasets. Exomiser, CADD and Condel did not score or rank some disease-causing variants at all. For the variants that were ranked, the average rank of the disease-causing variant provided by Exomiser was 15.6, CADD was 12.7 and Condel was 13.1. Exomiser outperformed CADD and Condel in placing more disease-causing variants within the top 5 (53% vs. 36% and 33% respectively). Clinicians included 40 of the 48 WES diagnoses in their a priori list of differential diagnoses (83%). The lists generated by PhenoTips and Phenomizer contained 14 (29%) and 18 (37.5%) of these diagnoses respectively. *Conclusions*: These results highlight the benefits of structured phenotyping and clinically-driven variant prioritization in increasing the efficiency of WES data analysis.

Oral 3
EXOME SEQUENCING HAS HIGHER DIAGNOSTIC YIELD COMPARED TO DISEASE-SPECIFIC PANELS IN 145 CHILDREN SUSPECTED OF HAVING MONOGENIC DISORDERS

Oliver Dillon[1], Zornitza Stark[2,3], Belinda Chong[2], Dean Phelan[2,3], Miss Gemma R Brett[2,3], Miss Emma Creed[3], Maie Walsh[2,3], Lilian Downie[2,3], David J Amor[1,2,3], Ravi Savarirayan[1,2,3], George McGillivray[2,3], Alison Yeung[2,3], Heidi Peters[3,4], Susan Robertson[4], Aaron J Robinson[4], Ivan Macciocca[2,3], Natalie Thorne[5], Clara Gaff[3,5], Susan M White[1,2,3], Tiong Yang Tan[1,2,3]

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Background: With the falling cost of exome sequencing, its worth in clinical diagnostics is increasingly evident. In patients for whom exome sequencing is considered, the alternative testing option is a commercial gene panel. *Objective:* We sought to compare the diagnostic yield of exome sequencing against hypothetical disease-specific gene panels in 145 prospectively recruited children suspected of having a monogenic disorder. *Methods*: We undertook exome sequencing with targeted phenotype-driven analysis in all children. At recruitment, each child's primary clinician was required to report the alternative testing options being considered in each case, if an exome were not available. In those diagnosed by exome sequencing, we analyzed the alternative test options to determine if the causative gene would have been identified. For each panel, we selected three commercial providers for analysis. We also evaluated the costs of alternative testing options compared to exome sequencing. *Results*: Clinicians proposing children for exome sequencing included pediatric neurologists, metabolic physicians, and clinical geneticists. The majority of children had dysmorphic features with congenital anomalies, or a neurometabolic disorder. Specific disease subgroups included skeletal dysplasias, eye, gastrointestinal or dermatological disorders. Overwhelmingly, exome sequencing was superior to gene panels in identifying the causative mutation. This was particularly evident in children with less specific phenotypes or dual diagnoses. *Conclusions*: We found that exome sequencing has higher diagnostic yield and is a more cost-effective strategy compared to a gene panel. Our data also provide insights into which children are most likely to benefit from exome sequencing over a gene panel.

Oral 4
THE GENOMIC AUTOPSY: USING WHOLE GENOME SEQUENCING TO SOLVE COMPLEX FETAL AND NEONATAL PRESENTATIONS

Christopher Barnett[1], Alicia Byrne[2,3], Lynette Moore[4], Jill Lipsett[4], Nicholas Manton[4], Yee Khong[4], Sui Yu[2], Marcel Dinger[5], Babic Milena[2,3], Peter Brautigan[2,3], Quentin Schwartz[3], P Thomas[6], Christopher Hahn[2,3], F Feng[6,7], Andreas Schreiber[6,7], Karin Kassahn[2,3], Hamish Scott[2,3,6,7]

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Background: Congenital abnormalities are the most frequent reason for mid-term stillbirth and termination of pregnancy. Unexplained late fetal deaths in utero, or in the newborn period, affect ~4/1000 births. Formal post-mortem examination is performed in these

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settings in South Australia in ~60% of cases (200/year), but despite this no definitive cause of the congenital abnormalities or death is found in 25–50% of cases. *Aim:* To use whole genome sequencing (WGS) to identify genetic causes of fetal and newborn abnormalities that result in termination of pregnancy, death due to congenital abnormalities, death in utero or death in the newborn period, in view to providing families with answers regarding cause and recurrence risk. *Methods*: WGS will be performed on 40 samples per year for 3 years, using the IlluminaHiSeq X Ten System. High priority cases are fetuses with congenital abnormalities with consanguineous parents (proband sample only); fetuses with multiple malformations; and unexplained fetal/newborn death (trio samples). Tertiary bioinformatics and primary functional assays will be used to confirm causality of variants. *Results*: This project is in its first year. Pilot data will be presented from the first WGS's performed, with specific focus on our discovery of a new autosomal recessive polycystic kidney disease gene, leading to a successful reproductive outcome for a family.

Discussion: Genomic autopsy using WGS offers enormous potential as an adjunct to traditional autopsy in providing accurate genetic counseling for families who have experienced pregnancy loss, death in utero, termination of pregnancy or death in the newborn period.

Oral 5
COST-EFFECTIVENESS OF THE DIAGNOSTIC WHOLE EXOME SEQUENCING APPROACH IN EPILEPTIC ENCEPHALOPATHY

Rani Sachdev[1,2], Elizabeth E. Palmer[2,3], Deborah Schofield[5,6], Rupendra Shrestha[5], Tejaswi Kandula[1,2], Rebecca Macintosh[1], Hugo Sampiao[1,2], Ian Andrews[1,2], John Lawson[1,2], Alexandra Johnson[1,2], Michael Cardamone[1,2], Michelle Farrar[1,2], William Lo[4], George Elakis[4], Ying Zhu[3,4], Michael Buckley[4], Marcel Dinger[6], Mark Cowley[6], Edwin P Kirk[1,2,4], Tony Roscioli[1,6], Ann Bye[1,2]

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Diagnostic whole exome sequencing (ES) is rapidly becoming integrated in clinical practice. Comparison of the ES approach to the previous 'traditional' testing approach has been repeatedly postulated to be cost-effective, mainly due to improved diagnostic yield and the potential to avoid an invasive and expensive 'diagnostic odyssey'. However, there is a paucity of health costing data to support this assertion. We present a comprehensive health-costings comparison for a well phenotyped cohort of 32 patients with epileptic encephalopathy (EE), using a counterfactual model, of a 'trio ES' model and 'traditional' diagnostic approach. EEs are severe epilepsies impacting cognition in which rapid establishment of etiology is important; however, traditional diagnostic approaches are invasive and expensive because of genetic heterogeneity and limited genotype-phenotype correlation. The cohort comprises EE patients seen at the Sydney Children's Hospital, born between 2000 and 2014, who remained undiagnosed after 'first-tier' testing. We determined the diagnostic yields (2/32;6.2% for the 'traditional' arm compared to 18/32;56.2% for the 'trio ES' arm), the comparative costs per patient ($11,937 'traditional arm'; $9,550 'trio ES' arm) and per diagnosis ($190,999 per diagnosis 'traditional' arm and $16,978 'trio ES' arm). We also present an analysis of projected diagnostic yields and costs for a variety of commercial trio exomes and EE panels. This study uniquely compares the diagnostic yield and cost of an ES and traditional approach for EE, and has important health policy implications for the diagnosis of Mendelian conditions in the next generation sequencing age.

Oral 6
USING MASSIVELY PARALLEL SEQUENCING TO DETERMINE THE GENETIC BASIS OF LEIGH SYNDROME, THE MOST COMMON PAEDIATRIC MITOCHONDRIAL DISORDER

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Aim: To identify the maximum diagnostic yield of massively parallel sequencing (MPS) in patients with Leigh syndrome (LS), the most common pediatric mitochondrial disease. *Background*: LS is a neurodegenerative disorder caused by mutations in >75 genes, encoded by both mitochondrial (mt) and nuclear DNA, with maternal, autosomal recessive or X-linked inheritance. This study focused on a published cohort of 67 patients with LS or Leigh-like disease. *Methods*: DNA from all 33 patients lacking a genetic diagnosis underwent whole exome sequencing supplemented with mtDNA baits, followed by targeted analysis of ~2200 genes (known and candidate mitochondrial disease genes, and differential diagnosis genes). Variants were identified using GATK Best Practices. Functional effects of rare variants were determined in silico, and through analyzing RNA and protein extracted from patient tissue and cells. *Results*: Pathogenic variants in 11 genes were identified in 16 of 33 patients, including multiple novel mutations. Careful analysis of MPS data, supplemented with identification of copy number variants using ExomeDepth, enabled genetic diagnosis where routine filtering yielded no candidates. We have now established the genetic basis in 75% of the total cohort (67 patients), including 34 of 35 LS patients and 16 of 32 Leigh-like patients. Possible genetic diagnoses, including in differential diagnosis genes, are under evaluation in 10 patients. *Conclusions*: Our results show that MPS can potentially identify the genetic basis in nearly 100% of patients with tightly defined LS, despite marked genetic and clinical heterogeneity. They also emphasize utility of a broader gene list, particularly in atypical patients.

Concurrent Session 10 — Submitted Orals

Oral 7
MAINSTREAMING GENOMICS — A THEORY-INFORMED SYSTEMATIC REVIEW OF CLINICIANS' GENETIC TESTING PRACTICES

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Background: Advances in genomic tests have increased technical efficiency and sensitivity of variant detection. Incorporating new tests into existing practice involves a change in clinical practice and a significant lag has previously existed between development of a genetic test and its adoption into mainstream healthcare. Lessons from monogenetic testing may help us anticipate clinicians' needs and concerns towards offering more comprehensive genomic tests, facilitating the effective introduction of such tests into mainstream healthcare. *Aim:* To identify factors affecting

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appropriate use of genetic tests by non-genetic-trained clinicians through a systematic review grounded in behaviour change theory. *Methods*: Studies which investigated non-genetic-trained clinicians' experience with offering genetic tests were identified from five electronic databases. These were critically appraised and using content analysis, were mapped to the Theoretical Domains Framework (TDF). *Results*: Twenty-five studies met inclusion criteria. The majority were conducted in the United States, used quantitative design, and investigated cancer genetic testing. Many had low response rates, and survey design lacked a theoretical basis. TDF factors identified which may impact upon clinicians' decisions to offer genetic tests included: knowledge, genetic test factors (uncertainty, incidental results), patient factors, organizational factors, professional factors, and ethical, legal, social and systemic factors. *Conclusions*: Using the TDF, we have produced a comprehensive overview of factors influencing clinicians' testing decisions, identifying areas for possible change to support mainstreaming genomic testing. Our findings demonstrate that more than education is required to incorporate new tests into clinical practice, and further theory-based research is needed to inform the successful introduction of genomic testing.

Oral 8
'WHAT DOES THIS RESULT MEAN FOR ME?' EXPERIENCE WITH CHANGING INTERPRETATION OF COPY NUMBER VARIANTS ON THE X CHROMOSOME 2008–2015 AND CHALLENGES IN GENETIC COUNSELING

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Chromosomal microarray (CMA) is considered a standard 'first-line' investigation for the cause of intellectual disability (ID) and autism spectrum disorder (ASD), and is increasingly requested for a diverse range of indications including in the prenatal setting. The detection of variants of uncertain clinical significance (VOUS), especially on the X chromosome, results in a substantial clinical dilemma. Clinicians are often uncertain how to best counsel the individual or family, or further investigate the significance of findings. The Genetics of Learning Disability (GOLD) Service is a unique clinical genetics service that has seen over 600 families with all forms of familial ID. Our referral criteria include individuals with VOUS/potentially pathogenic CNV on the X chromosome. Our service benefits from the ability to perform detailed segregation analysis and collaborative links with diagnostic and research genetics laboratories. We present a retrospective case series of 40 families seen through our service since 2007 who had a CNV identified on the X chromosome. 75% ($n = 30$) of the initial laboratory reports classified the CNV as VOUS, with 25% ($n = 10$) classifying the CNV as pathogenic. After further investigation, and reclassification of 28 results, we currently regard 45% (n=18) as pathogenic/likely pathogenic, 47% ($n = 19$) as benign/likely benign, and only 8% ($n = 3$) as VOUS. We report the clinical and molecular strategies that have been most helpful in assessing variant pathogenicity and highlight particular challenges in genetic counseling regarding complex and uncertain genetic results, using a recent prenatal case as an example of how families utilize revised reporting of CMA.

Oral 9
GENETIC COUNSELING CHALLENGES WITH REPRODUCTIVE GENETIC CARRIER SCREENING FOR CYSTIC FIBROSIS, FRAGILE X SYNDROME AND SPINAL MUSCULAR ATROPHY: EXPERIENCE WITH 10,000 PATIENTS

Alison Archibald[1,2,3], Katrina Scarff[1], Melanie Smith[1], Justine Elliott[1], Clare Hunt[1], Zoe McDonald[1], Caitlin Barns-Jenkins[1], Chelsea Holt[1], Karina Sandoval[1], Vanessa Siva Kumar[1], Lisa Ward[1], Shannon Cowie[1], Trent Burgess[1,2], David Amor[1,2,3,4], Eppie Yiu[2,3,4], John Massie[2,3,4], Desiree Du Sart[1,2], Damien Bruno[1,2]

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For the past 3 years Victorian Clinical Genetics Services (VCGS) has been offering the Reproductive Genetic Carrier Screen (RGCS) for: cystic fibrosis (CF), fragile X syndrome (FXS) and spinal muscular atrophy (SMA). This novel screen is offered due to high carrier frequencies, the significant impact on affected individuals and their families, accurate tests and research indicating support for screening. RGCS is offered in general practice, obstetrics, fertility and genetics settings in pre-pregnancy and/or early pregnancy. Carriers are offered genetic counseling and partner testing with prenatal testing available to pregnant couples at increased risk for any of the conditions. Appointments with physicians specializing in the condition are also offered. Screening of 10,000 people has revealed 516 carriers of one or more conditions (5.2%; 1 in 19): 293 CF (56%), 28 FXS (5%), 204 SMA (39%), including 9 carriers of 2 conditions. At least 86% of partners of CF and SMA carriers were tested. Thirty-seven couples were at increased risk of having a child with one of these conditions (11 CF, 25 FXS and 1 SMA) and 25 were pregnant. Of these, 22 opted for prenatal diagnosis (6 affected: 3 CF, 2 FXS, 1 SMA). Increased risk couples utilized prenatal diagnosis and/or PGD for subsequent pregnancies. Genetic counseling challenges will be discussed including: cascade testing, managing 'low' FXS permutation results (<60 CGG repeats), and the clinical utility of SMN2 testing in prenatal diagnosis for SMA carrier couples. Successful carrier screening for these conditions requires the availability of appropriate genetic counseling support.

Oral 10
IMPACT OF A POSITIVE HYPERTROPHIC CARDIOMYOPATHY GENE RESULT IN ASYMPTOMATIC FAMILY MEMBERS

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Aim: When a genetic diagnosis is made in a hypertrophic cardiomyopathy (HCM) proband, first-degree relatives are offered cascade genetic testing in addition to clinical screening. Adult family members with no clinical evidence of HCM who receive a positive genetic test result are considered 'at-risk', but no therapies are initiated in the absence of a phenotype. This study explored the experience of genetic testing for this new group of 'genotype positive, phenotype negative' (G+P-) patients. *Method:* Nineteen G+P- patients were recruited from a specialist genetic heart disease clinic. Semi-structured interviews were conducted face to face or by phone, and transcribed audio-recordings were coded using

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Framework Analysis. *Results*: Participants reported the main benefit of genetic testing was for the next generation, and worried more about children than themselves. Genetic test results were viewed as beneficial yet had multiple subtle but potentially important impacts on participants' lives, including: avoiding strenuous exercise, monitoring their heart rate, and increased awareness of heart symptoms. Advice from medical professionals was often contradictory, leading to uncertainty about risk and management. Implications for insurance and family planning related to whether participants self-identified as having a current medical condition/disease. *Conclusion*: While genetic testing has clear potential to benefit relatives who receive a negative result, the meaning of a positive result in the absence of clinical signs or prevention strategies is unclear, and can lead to misconceptions about disease status and management. Better understanding of the patient experience is needed to inform pre-test counseling and post-result clinical management of families.

Oral 11
GENOMES AND PREGNANCY, THE GAP STUDY: PROVIDING CHOICE OF FETAL GENOMIC RESULTS TO WOMEN HAVING PRENATAL DIAGNOSIS

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Background: Use of chromosome microarrays for prenatal diagnosis can detect copy number variants of unknown or uncertain significance (VOUS). The Genomics and Pregnancy study (GaP) aims to find out if parents want information on VOUS in pregnancy. *Methods*: Women having prenatal diagnosis were recruited, but not when there was report of fetal abnormality on ultrasound. Participants were given a study-specific decision aid and asked to choose between receiving targeted (pathogenic only) or extended (plus VOUS) fetal genomic information. Two surveys were completed, one before the procedure assessing decisional conflict, state/trait anxiety, intolerance of uncertainty and health literacy. Another survey, sent approximately ten days after receiving the result, assessed decisional regret, satisfaction with decision and state anxiety. *Results*: Of 111 participants, 40.5% chose targeted and 59.5% chose extended analysis. Choice was not associated with maternal age, parity, religion, ethnicity, education, and financial situation; however those trying to conceive for $\geq$12 months and using fertility treatments were significantly more likely to choose extended (78% and 92% respectively). Women choosing extended had significantly higher trait anxiety (mean score of 39.5 (*SD* 9.3)), compared to women who chose targeted (mean score 36.2 [*SD* 6.8]), $p < .05$. *Conclusion*: While current practice typically involves extended analysis, GaP demonstrates this does not reflect the true preference of those having prenatal diagnostic testing when there are normal ultrasound findings. Provision of choice in pregnancy about reporting of genomic results is ideal; if laboratories are prepared to offer such choice, decision-support methods before collection of genetic material could be adopted to facilitate this.

Oral 12
GENETIC RISK FACTORS FOR VULVAR CANCER IN YOUNG INDIGENOUS WOMEN IN ARNHEM LAND

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Background: Vulvar cancer is usually rare, and occurs most often in postmenopausal women. Among young (<50 years) Indigenous women living in remote Aboriginal communities in Arnhem Land; however, the incidence of this malignancy is more than 70 times the national Australian rate for the same age group. Previously, we found that neither excess human papillomavirus (HPV) incidence nor a particularly virulent strain of HPV could explain the very high incidence of vulvar cancer in this population. Reports from the Gynaecology Outreach Service that cases appeared to cluster in family groups suggested a genetic susceptibility, either to the effects of HPV or another cause of vulvar cancer. *Methods*: To investigate the role of genetic risk factors, 30 cases and 61 controls, matched on age and community of residence, were recruited to the study. DNA was extracted from saliva samples, and genotyped to provide information on approximately 2.5 million variants. These data were analyzed using both genome- wide association and identity-by-descent techniques. *Results*: We found clear evidence for the involvement of a genetic risk factor predisposing this population to vulvar cancer, and identified three genomic regions of interest. *Discussion*: Bioinformatic analysis prioritised biologically plausible candidate genes within these regions. Sequencing and functional studies to further elucidate the role of genetic variants in the etiology of vulvar cancer are currently underway. This is the first genetic study of this population, and these findings continue to inform health care delivery in Arnhem Land, especially vaccination policy and screening strategies.

Australasian Association of Clinical Geneticists SIG Meeting

KBG SYNDROME: AN AUSTRALIAN EXPERIENCE

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A syndrome of intellectual disability, macrodontia of the upper central incisors and distinct craniofacial dysmorphisms was first described in 1975 by Hermann et al. and KBG syndrome was coined based on the initials of the affected families' surnames. In 2011, Sirmaci et al through whole exome sequencing identified heterozygous mutations in the ANKRD11 gene in affected individuals. Since then, around 60 cases have been described in the literature with the expansion of the clinical phenotype. The role of mutations in affecting degradation of the mutant protein with a possible dominant negative mechanism has been delineated (Walz et al., 2015). Here we present an Australian cohort of 9 KBG affected individuals, all with pathogenic mutations in the ANKRD11 gene on chromosome 16 confirmed on DNA sequencing. Data was collected from participating geneticists across Australia. The clinical phenotype was defined according to a proforma based on the diagnostic features described by Skjei et al. DNA sequencing was performed using individual HGSA accredited

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laboratories. Mutations were analyzed according to effect on protein based on USCS genome browser and pathogenicity was determined based on ACMG guidelines. Several novel heterozygous variants have been described and the genotype-phenotype correlations have been explored. These cases highlight the need for thorough examination and investigation of the dental and skeletal systems in the approach to syndromic intellectual disability. KBG remains an under-diagnosed entity in the Australian population and exhibits intra- and interfamilial variability. The description of further cases of KBG syndrome is needed to further delineate this condition.

MUTATIONS IN CDC45, ENCODING AN ESSENTIAL COMPONENT OF THE PRE-INITIATION COMPLEX, CAUSE MEIER-GORLIN SYNDROME AND CRANIOSYNOSTOSIS

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DNA replication precisely duplicates the genome to ensure stable inheritance of genetic information. Impaired licensing of origins of replication during the G1 phase of the cell cycle has been implicated in Meier- Gorlin syndrome (MGS), a disorder defined by the triad of short stature, microtia and a/hypoplastic patellae. Biallelic partial loss-of-function mutations in multiple components of the pre-replication complex (preRC; ORC1, ORC4, ORC6, CDT1 or CDC6) as well as de novo activating mutations in the licencing inhibitor, GMNN, cause MGS. We have identified mutations in CDC45 in 15 affected individuals from 12 families with MGS and/or craniosynostosis. CDC45 encodes a component of both the pre-initiation (preIC) and CMG helicase complexes, required respectively for initiation of DNA replication origin firing and ongoing DNA synthesis during S-phase itself, hence is functionally distinct from previously identified MGS genes. The phenotypes of affected individuals range from syndromic coronal craniosynostosis to severe growth restriction, fulfilling diagnostic criteria for Meier-Gorlin syndrome. All mutations identified were biallelic and included synonymous mutations altering splicing of physiological CDC45 transcripts, as well as amino acid substitutions expected to result in partial loss of function. Functionally, mutations reduce levels of full-length transcripts and protein in patient cells, consistent with partial loss of CDC45 function and a predicted limited rate of DNA replication and cell proliferation. Our findings therefore implicate the preIC as an additional protein complex involved in the etiology of MGS, and connect the core ce nome replication with growth, chondrogenesis and cranial suture homeostasis.

Australasian Society of Diagnostic Genomics SIG Meeting

INCIDENCE OF GONADAL MOSAICISM IDENTIFIED BY MICROARRAY TESTING OF PARENTS AND CHILDREN

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The current dogma in gonadal mosaicism is to counsel for a less than 1% recurrence risk. It is known that highly penetrant autosomal dominant conditions may be masked in phenotypically unaffected parents by somatic mosaicism. Recent literature shows that somatic mosaicism in an unaffected parent maybe higher than previously reported. If so, the risk of recurrence (RR) may be significantly underestimated and parents falsely reassured. The aim of our study was to assess parental mosaicism to generate our own gonadal mosaicism risk and replicate recent published results. We performed a retrospective study in all patients referred to the Clinical Genetics service at a metropolitan hospital over a 1-year period to quantify incidence parental somatic mosaicism. The main inclusion criteria was a prenatal micro array via CVS or amniocentesis, and a micro array test on at least one of the parents if positive or two parents if negative. The micro array report itself was used to classify a parent as mosaic for a specific change, identified as non-mosaic in the foetus. We report out findings in 1,109 individuals referred in 2015, of whom 265 were referred for prenatal assessment. As per previously reported data, we expected a 4% RR versus the previously quoted less than 1% RR.

ARRAY CGH IN PRENATAL DIAGNOSIS: A REVIEW OF VARIATIONS OF UNKNOWN SIGNIFICANCE REPORTING, TIME TO LOOK FOR AN ALTERNATIVE APPROACH?

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In Australia, Array CGH has replaced conventional cytogenetic analysis as the first line of investigation in prenatal diagnosis. One drawback is the detection of VoUS (Variations of Unknown Significance). There are now well established international guidelines for test indications, result interpretation and report writing for prenatal chromosomal analysis by Array CGH. Many laboratories take an approach to process all the prenatal samples by both FISH and Array CGH. We present data from the cytogenetics department at Monash Health, where array CGH was introduced in 2013 with a similar policy. There was a total of 850 prenatal specimens tested to date and 100 reports (11.7%) with VoUS issued, with parental studies completed in the majority of them. We review the indications and fetal outcome for these cases. The internationally recommended approach of restricting array CGH testing to selected high risk cases with abnormal ultrasound scan and/or nuchal translucency of more than 3.5 mm will be discussed. A new processing workflow for prenatal chromosome testing will be proposed. Interpretation criteria's for neurosusceptibilty loci in prenatal samples will be reviewed. The existing data will be compared with the proposed workflow. The clinical and economic impact of the proposed approach with special emphasis in a public hospital setup will be summarized.

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UTILITY OF SNP MICROARRAY FOR ELUCIDATING CAUSATIVE RECESSIVE GENES AND FOR CREATING PATIENT SPECIFIC CANDIDATE GENE LISTS FOR WHOLE EXOME SEQUENCING

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The introduction of chromosome microarray (CMA) into diagnostic genetic testing instigated a new era of genetic interpretation, in particular for disorders caused by copy number variants with incomplete penetrance and variable expressivity. Through the use of SNP-based CMA, long continuous stretches of homozygosity (LCSH) have provided an additional clinical resource for identifying genes associated with recessive disorders. LCSH are detected in individuals with consanguineous parents as expected, but also in individuals from apparently outbred populations. In our cohort of 60,000 individuals, approximately 10% have at least 1 LCSH greater than 5 megabases in length. We will showcase, using a range of clinical examples, how the medical scientist can work with the clinical geneticist/ medical specialist to successfully identify the pathogenic mutation in an affected individual or multiple family members. The approach taken can vary depending on the number of affected and unaffected family members, the size of the proposed candidate gene list, and the genomic percentage of the LCSH. If a strong candidate gene has been identified with this approach, as in the majority of the examples presented here, single gene sequencing can confirm causative homozygous mutations. If a single strong candidate gene does not emerge, then review of the LCSH gene content can be invaluable in generating candidate gene lists to direct the analysis of whole exome and whole genome data, either in the clinical setting or as part of gene discovery projects.

APPLICATION OF NGS FOR THE INVESTIGATION OF ABNORMALITIES OF THE Y CHROMOSOME

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There are a number of genes involved in infertility; we have developed a custom designed, targeted panel with amplicons for coding regions covering genes for the investigation of both males and females. The gene covered on the Y chromosome include SRY, ZFY, amelogenin Y, USP9Y, EIF1AY, BPY2 and DAZ. The Y chromosome is unique in that it does not have a homologue for complete pairing and recombination at meiosis. It shows size variability due to differing amounts of heterochromatin in the q arm. It also contains regions of palindromes and inversions that are capable of recombining, resulting in duplications and deletions. Deletions in the AZF region of Yq are associated with absent or reduced sperm production. Best practice guidelines to date (2013) only recommend looking at micro satellite markers for deletions in this region. Three of our patients who have been shown to be deleted for AZF a,b and c by microsatellite markers, have been shown not to be deleted for any of the relevant genes in these regions by NGS and are also FISH positive for probes for the three regions. One case of a 46,XY female has been shown not to have any base pair alterations in SRY suggesting her androgen insensitivity is not related to SRY. One case of a cytogenetic 46,XX male was initially detected by NGS as he had only SRY and amelogenin X present. Subsequent cytogenetic studies determined a 46,XX karyotype and FISH showed SRY translocated to Xp.

IDENTIFYING NOVEL GENETIC CAUSES OF 46,XY DISORDERS OF SEX DEVELOPMENT USING TARGETED SEQUENCING TECHNOLOGIES

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Background: Disorders of sex development (DSDs) are congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. DSDs include a wide range of anomolies and together account for 7.5% of all birth defects. Indeed, 1 in 4,500 babies worldwide is born with significant ambiguous genitalia. Currently only 30% of all DSDs are diagnosed at the genetic level. In particular 46,XY DSDs (including patients with gonadal dysgenesis or under-virilisation) have a poorly defined etiology, perhaps due to gaps in the understanding of the molecular pathways required for testis development. *Methods*: To address these gaps we have recruited a cohort of around 420 46,XY DSD patients, including patients with gonadal dysgenesis, androgen insensitivity and hypospadias. We are screening these patients for novel mutations in genes using a variety of methods including a targeted massively parallel sequencing panel of around 1,000 known or candidate DSD genes, whole exome sequencing and a targeted DSD CGH array. *Results*: We have thus far analyzed 270 46,XY patients. A likely pathogenic variant in a diagnostic DSD gene has been found in 45% of these patients illustrating the diagnostic power of our screening methods. These include novel mutations in rare DSD genes such as GATA4 and FOG2. In addition, we have identified several candidate DSD genes, including a negative regulator of the WNT signaling pathway and androgen receptor interacting proteins. Functional testing is underway and we will present the mounting evidence that these genes play a role in the development of testis and in DSD.

NEXT GENERATION SEQUENCING IN PATIENTS WITH OVERGROWTH

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Background: Overgrowth is a sign in clinical genetics practice used to help diagnose a group of heterogenous conditions where excessive growth, developmental delay, dysmorphic features, and increased risk of neoplasia are prominent. In this study, overgrowth was defined as requiring at least two of three parameters (height, weight, head circumference) significantly greater than the 97th centile. *Aims and hypotheses:* It was hypothesized that due to genetic heterogeneity and subtle phenotypic distinctions, overgrowth syndromes are difficult to clinically diagnose and that a next generation sequencing (NGS) gene panel may improve rates of diagnosis. Another aim was to allow for phenotypic expansion of some of the overgrowth syndromes. *Methods*: An audit of all patients seen over a 5-year period at Hunter Genetics occurred to determine current diagnostic rates. 24 undiagnosed patients identified by the audit were then retrospectively recruited and an additional 14 patients were prospectively recruited. A NGS panel examining 30 genes was applied to the cohort. *Results*: The audit identified that 21/61 overgrowth patients had a secure clinical or molecular diagnosis and that most of these diagnoses were chromosomal deletions or duplications detected by array CGH while few syndromic diagnoses were made. The NGS panel found 5 variants of uncertain significance including a family with a SETD2 variant and a family with both a PTEN and PTCH1 variant. These findings expand the phenotypic possibilities of mutations in these genes. *Conclusion*: Our findings show that overgrowth is a

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non-specific clinical sign where achieving a molecular diagnosis is challenging.

GENOTYPER: AN ALIGNMENT FREE APPROACH FOR THE IDENTIFICATION OF VARIANTS IN RAW MASSIVELY PARALLEL SEQUENCING DATA

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Variant calling in massively parallel sequencing (MPS) data is virtually always preceded by multiple bioinformatic processing steps, including the alignment of millions of sequencing reads to a reference genome. Due to the vast amount of data generated and the complexity of the task, by necessity the utilized alignment algorithms have to trade off the accuracy of read placement against the speed of the analysis. While most of the currently available tools are doing an excellent job, even very low error rates can result in false positive variant calls (alignment artefacts), which are not actually present in the raw data. We have developed and tested a tool (Genotyper) that is able to quickly and reliably scan sequencing raw (FASTQ) data for previously known variants. While Genotyper is not able to identify novel variants in the data, it is designed to take results generated by a conventional variant calling pipeline and confirm their presence in the raw data, thereby increasing the specificity of variant calling through alignment artefact identification. At the same time, it can be used for fast identity checking of MPS data against known patient SNPs before running expensive analyses. Perhaps most interestingly, our tool can be used to quickly screen every MPS dataset for known pathogenic variants (e.g., ClinVar, HGMD) and thereby not only increase the specificity, but also the speed and sensitivity of pathogenic variant identification.

IMPLEMENTATION OF A 174-GENE CAPTURE PANEL FOR GENETIC DIAGNOSIS OF CARDIAC DISORDERS

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Background: The Department of Diagnostic Genomics at PathWest provides molecular diagnostic services for a range of genetic disorders. Since 2012, the Department has begun the introduction of Massively Parallel Sequencing (MPS) technologies to improve the efficacy and efficiency of these services. In June 2015 we commenced the use of a specialist gene panel for the analysis of a broad range of cardiac disorders. *Aim*: To examine the efficacy of MPS analysis for the genetic diagnosis of cardiac disorders. *Methods*: Patient samples were examined using the 174-gene Illumina TruSight Cardio Sequencing Kit, which utilises capture probes for isolation of target sequences. Libraries were sequenced on an Illumina MiSeq Desktop Sequencer with alignment and variant calling performed using BWA-MEM and GATK, respectively. Variant analysis was performed with Cartagenia Bench Lab NGS and Alamut Visual. *Results*: The Cardio Sequencing Kit yields at least 20-fold coverage for greater than 99% of target sequences, with a mean coverage across all currently tested samples of 400-fold. Validation with known control samples demonstrated efficacy in detection of single nucleotide variants and indels of up to 36bp in length. Complete analysis of 150 diagnostic patient samples has detected a clinically significant variant in 23% of cases, with 30% of structural disorders yielding a clinically significant variant. *Conclusion*: The use of a specialist gene panel for cardiac disorders has enabled the efficient analysis of a large range of relevant genes and proved highly effective in the detection of significant genetic variants.

TRIAGING COMPLEX CASES FOR GENETIC TESTING IN SOUTH AUSTRALIA: A MULTIDISCIPLINARY TEAM APPROACH

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New genetic testing platforms offer much promise, but remain a limited resource in diagnostic settings. To maximize clinical utility, our diagnostic service has implemented a structured triage process. Tests are determined to be either 'standard testing' or 'case requiring review' (complex or panel precedent cases). The review process uses a multidisciplinary team (MDT) forum, with structured case presentations and decision criteria to assist determination of the most appropriate testing. The review process includes consideration of management implications, evidence supporting genetic testing indication and utility, test availability, service capacity and in-house expertise, as well as expected turnaround time. A recommendation for each case is formed after open and robust discussion between the MDT meeting members (primary clinicians, pathologists, medical scientists and bioinformaticians). In 18 months, next-generation sequencing has replaced classical genetic testing as the platform of choice for more than 800 standard tests (especially for large genes). In addition, the consensus-based, open discussion MDT platform has reviewed 80 complex clinical cases over this period. The majority of complex cases have been pediatric patients, with the greatest number referred from clinical geneticists, however immunologists, neurologists, cardiologists, metabolic, renal and general physicians have also been represented. a summary of the MDT system, with range of outcomes, phenotypes and results encountered will be presented. This approach reflects a paradigm shift in clinical review meetings, where embedding medical scientists with pathologists and primary physicians in an active clinical conversation maximises the utility of diagnostic services and assists best clinical outcome for patients.

A CUSTOM GENE PANEL FOR INTERROGATING PEDIATRIC OVERGROWTH DISORDERS AND TUMOUR PREDISPOSITION

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The Genetics and Molecular Pathology laboratory at Monash Health is the predominant Australian testing laboratory for pediatric overgrowth disorders associated with increased cancer risk in childhood, including Beckwith Wiedemann syndrome (BWS) and hemihypertrophy (HH). Cascade testing typically involves SNP microarray, methylation analysis of imprinting centres on 11p15.5 and CDKN1C (P57) mutation screening.

Rare point mutations in NSD1, NLRP2, DNMT1 and ZFP57 have been described in BWS and like disorders as well as deletions and insertions within the 11p15.5 imprinting centres IC1 (H19/IGF2) and IC2 (KCNQ1OT1/CDKN1C). Tumor risk is increased in most genetic and epigenetic subtypes of BWS and HH however degree of risk and tumor type varies between groups. Parents of affected children are often understandably anxious to know

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the recurrence risk for these conditions and as the number of childhood cancer survivors increases, the possibility for transmission of a causative mutation is becoming an increasingly important issue. To improve our capacity to detect predisposing mutations in BWS, HH and in the pediatric tumors that have been described in these conditions, we have designed a gene panel comprising 37 genes as well as intergenic regions spanning imprinting centres on 11p15.5 and 11p13. We have used the Haloplex target enrichment system with sequences run on an Illumina MiSeq. We have performed pilot testing to show that the panel has clinical utility and demonstrates excellent sequence coverage of the 11p imprinting centres. Analysis of results to date has revealed novel mutations including OCT-4 binding site disruption in IC1 and subregions of homozygosity.

A NEW APPROACH TO MEASURING BONE MARROW TRANSPLANT CHIMERISM BASED ON UBIQUITOUS, HIGHLY HETEROZYGOUS COPY NUMBER VARIATION AND DIGITAL DROPLET PCR

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Background: Chimerism analysis is used for assessment of engraftment, minimal residual disease and relapse in allogenic bone marrow transplantation (BMT). Serial analysis is also used to guide treatment intensity so as to maximize graft-versus-tumour effect and minimize graft rejection, opportunistic infection and graft-versus-host disease risk. *Aim*: To develop a panel of DNA copy number deletion (CND) markers for monitoring any allogeneic bone marrow transplant, especially those with multiple or close relative donors and a highly sensitive and robust chimerism assay to potentiate early detection of relapse and minimal residual disease. *Methods*: The key advantage of the CND approach is the use of homozygous copy number deletions in either the donor or recipient to provide a 'zero background' for the assay and digital droplet PCR for absolute quantification. Unlike all other polymorphic markers in use (SNPs, indels, STRs), CNDs are monoallelic, a feature that provides significant improvements in quantification. *Results*: Validation studies indicate ready availability of multiple CND markers (at least 3 informative markers in 99% of typical unrelated donor-recipient transplants) and assay sensitivity down to 0.01% chimerism with good inter- and intra-assay reproducibility and concordance with SNP and FISH methods of chimerism analysis. *Discussion*: The assay is now in clinical use for routine transplants including measuring chimerism in genetically complex, multiple-relative donor transplants and on flow-sorted leukocyte subpopulations. The simplicity of this approach, combined with the advantages of ddPCR technology, recommend it as an improved approach to monitoring of allogeneic BMT chimerism.

LIMITATIONS OF PYROSEQUENCING FOR DETECTION OF SOMATIC MUTATIONS IN A CLINICAL SETTING

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Background: In December 2015, our laboratory implemented the use of CE-IVD marked Therascreen Kits for testing KRAS, BRAF and EGFR gene mutations in FFPE tissue. The PyroMark analysis software was implemented to assist with processing data; however, there have been three KRAS cases where it has either called the mutation incorrectly, or not at all. These cases were repeated using the PyroMark platform, and results confirmed by Sanger Sequencing. *Aim*: To investigate somatic mutations called incorrectly by the PyroMark analysis software. *Method:* DNA was extracted using the QiaSymphony tissue protocol, and amplified and sequenced using the Therascreen PyroMark kits as per the prescribed method. All samples were re extracted and repeated using the method above, and by Sanger sequencing on the ABI 3730 analyzer. Case 3, a particularly rare mutation, was repeated by both methods on normal tissue to exclude the possibility of a germline mutation. *Results*: Cases 1 and 2; software called as c.35G>T, found to be c.37G>T. Case 3: software failed to analyze, found to be c.36_38dup. Normal tissue was wildtype. *Conclusion/Discussion*: This highlights the importance of manually checking the program against the histogram when analyzing pyrosequencing. When relying on a software program that calls only common mutations, there is a chance that rarer mutations may be missed or called incorrectly. Rarer mutations at a lower level are difficult to confirm using other methodology, that is, Sanger sequencing has a sensitivity of ~20%, Pyrosequencing ~5-10%.

FAMILIAL LEUKAEMIA, THE NEXT GENERATION — REDEFINING FAMILIAL HEMATOLOGICAL RISK THROUGH THE AUSTRALIAN FAMILIAL HEMATOLOGICAL CANCER STUDY

Hamish Scott[1], Anna Brown[1], Devendra Hiwase[2], Andreas Schreiber[1], Jinghua Feng[1], Milena Babic[1], Nicola Poplawski[2], Graeme Suthers[2], Miriam Fine[2], Lesley Rawlings[2], Richard D'Andrea[1], Christopher Hahn[1]

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The Australian Familial Haematological Cancer Study (AFHCS) was founded in 2004 when only one familial hematological malignancy (FHM) gene was known, RUNX1 causing thrombocytopenia and predominantly an MDS/AML HM phenotype. Today, there are at least 12 known FHM genes. We have a still growing collection of over 80 families as well as access to large numbers of sporadic hematological malignancies (HM). Many of these families have now been solved through our identification of mutations in genes such as GATA2 and PAX5 and the characterisation of novel RUNX1, CEBPA and DDX41 families. Interestingly, phenotypic heterogeneity is now evident across families with the same gene mutated, presumably due to differential alteration of function caused by different mutations in the same gene. One example of this is our recent identification of a family with a lymphoma phenotype segregating with a novel mutation in DDX41 (p. R164W), where most other DDX41 families identified to-date have predominantly MDS/AML. Accumulating evidence also suggests that in addition to characterised mutations segregating in FHM, there are further genetic modifiers at play. First, the observation of anticipation in many families may suggest the introduction of additional pathogenic variants thus accounting for the decreasing age of diagnosis in subsequent generations. Second, phenotypic diversity and incomplete penetrance of phenotypes within and across families with identical mutations in the same FHM gene are readily observable. He presentation will provide an overview and an update of our work showing germline genetic variants contributing not only to FHM but also sporadic HMs.

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TRANSLATING RESEARCH IN TO THE PEDIATRIC ONCOLOGY CLINIC: A PERSONALISED MEDICINE TRIAL TO ASSESS THE FEASIBILITY AND CLINICAL VALUE OF A DIAGNOSTIC PLATFORM FOR IDENTIFYING NOVEL TARGETED THERAPEUTIC AGENTS FOR HIGH RISK PEDIATRIC AND AYA CANCER PATIENTS USING A MULTIDISCIPLINARY INTEGRATIVE APPROACH

Vanessa Tyrrell[1], Loretta Lau[1,2], Michelle Haber[1], Glenn Marshall[1,2], Carol Wadham[1], Emily Mould[1], Amit Kumar[1,3], Angela Xie[1], Richard Lock[1], Karen Mac Kenzie[1], Paul Ekert[1,4], Andrew Fellowes[3], David Ziegler[1,2], Toby Trahair[1,2]

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~1000 children in Australia are diagnosed with cancer each year, among the highest incidence Internationally (Baade et al., 2010British Journal of Cancer, 102 [1], and cancer remains the leading cause of death by disease in children. Most cancer chemotherapeutics used to treat childhood cancers have non-specific cytotoxicity to both normal and cancer cells, resulting in significant health care costs (20-25% of the work in children's hospitals in Australia). 30% of survivors will suffer one or more serious life-altering health conditions as a result of the toxicity of current treatments (http://curesearch.org/Childhood-Cancer-Statistics). A personalised medicine trial is being undertaken to assess the feasibility of a diagnostic platform for the identification of novel therapeutic agents for high-risk pediatric malignancies with expected overall survival $\leq$30%.

Patients' tumour and germline samples are being collected at diagnosis and/or relapse and analyzed using: (1) Genetic analysis (targeted molecular profiling [DNA, RNA], WGS, RNASeq); (2) In vitro high throughput drug sensitivity screening; (3) In vivo drug response testing using patient-derived xenograft models. Since the launch of the feasibility study, 24 children have been enrolled, and where sufficient and appropriate tissue samples have been available, methods described above have been performed, and results combined and correlated with clinical data. The proportion of patients where results inform an alteration of treatment leading to improved clinical outcome will be assessed. This study may provide the evidence that personalised cancer therapy has the potential to improve outcome and reduce treatment-related toxicities, and hence reduce the burden to the health care system.

Australasian Society of Genetic Counsellors SIG Meeting

PRENATAL GENOMIC SEQUENCING: HOW MUCH INFORMATION IS TOO MUCH?

Allison Werner-Lin

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The American College of Obstetrics and Gynecology considers prenatal chromosomal microarray analysis (CMA) an appropriate first-tier test following detection of an ultrasound anomaly. The increased diagnostic yield of CMA is, however, accompanied by the possibility of finding copy number variants (CNVs) of uncertain clinical significance, incomplete penetrance, or variable expressivity, with phenotypes ranging from apparently normal to severely affected. Carrying a pregnancy to term without understanding or knowledge of the full implications of an uncertain CNV may come at great emotional and financial cost to the parent and to the child. Little is known about the experiences of parenting an infant following such findings. Our team conducted semi-structured telephone interviews with 23 mothers of 6–12 month old infants diagnosed prenatally with a potentially pathogenic CNV to elicit perspectives on the child's health and development, support needs, and intent to share their child's results with others. Most mothers reported that their infants were developing typically (n = 24, 73%). Yet, the majority of mothers expressed ongoing concern about their child's development, leading a few to seek out early intervention or ongoing assessments by pediatricians. Approaches to parenting were stratified across three levels of intensity, ranging from perseverant vigil to unworried. All interviewees shared the result with the either the child's pediatrician, their relatives, and/or with friends. The few who did not cited fear of stigma, lack of understandings, an inability to explain the CNV, or presumptions that the child was not affected. Belief that a child is perpetually at risk may incite fear that cannot be completely assuaged due to the limits of our understanding of CNVs of unknown significance. And without any symptoms other than a positive test result, families remain in a state of prolonged uncertainty, physicians lack the diagnostic schema that permits clear conceptualization and action, and children may be perceived as vulnerable in ways that are unfounded. The potential for over-medicalization of the child's development heightens the risk of parental, and potentially of the physician's, perception that the child is vulnerable, and may come to shape the child's social experiences or identity.

GENOMICS: NEW WAYS OF THINKING FOR NEW TECHNOLOGIES

Paul James

Genetic Medicine, Royal Melbourne Hospital; Familial Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne, VIC, Australia.

In recent years clinical genetics has witnessed major technological changes involving a massive expansion in genetic sequencing capacity. As a result, the focus of researchers and clinicians has very quickly moved from single genes to whole genomes, and a 'new' clinical speciality of genomics has come into being. We are only now beginning to consider how the genomic information generated by these new technologies differs from more conventional genetic data and how this will impact on the practice of clinical genetics and genetic counseling. In this talk I will be considering these changes from the point of view the fundamental tool kit needed for clinical genomics, as well as reflecting more broadly on implications for the foundations of the way we practice.

IMPACT OF GENOMIC TECHNOLOGIES ON THE ROLE OF THE GENETIC COUNSELOR

Clara Gaff

The University of Melbourne and Melbourne Genomics Health Alliance, Melbourne, VIC, Australia

Although not yet available as a funded test, genomic sequencing is increasingly available to patients in Australasia. Some patients participate in gene discovery research, while others receive testing as part of programs identifying and addressing the barriers to the use of genomics in clinical practice. International experience has shown a direct impact of genomics on the profession of genetic counselors. In the United States, the introduction of genomics has led both to expanded roles and a shortage of genetic counselors. In the United Kingdom, profound changes to the genetic counseling training and registration process have been driven by the

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anticipated impact of genomics on their national health system. Locally, genetic counselors are playing key roles in the transition of genomic technologies from research to practice. As well as providing clinical genetic counseling, genetic counselors are trialing new roles, conducting research, educating other professionals and contributing to policy. Genetic counselors are therefore well placed to shape the way in which genomics is incorporated into the role of the genetic counselor. These themes will be explored as I consider the current impact and future role of genetic counselors in the era of genomic medicine.

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Abstracts From the 40th Human Genetics Society of Australasia Annual Scientific Meeting

Hobart, Tasmania

August 6–9, 2016

Poster Presentations

CANCER GENETICS

1. TRANSLATING RESEARCH IN TO THE PEDIATRIC ONCOLOGY CLINIC: A PERSONALIZED MEDICINE TRIAL TO ASSESS THE FEASIBILITY AND CLINICAL VALUE OF A DIAGNOSTIC PLATFORM FOR IDENTIFYING NOVEL TARGETED THERAPEUTIC AGENTS FOR HIGH-RISK PEDIATRIC AND AYA CANCER PATIENTS USING A MULTIDISCIPLINARY INTEGRATIVE APPROACH

Vanessa Tyrrell[1], Loretta Lau[1,2], Michelle Haber[1], Glenn Marshall[1,2], Carol Wadham[1], Emily Mould[1], Amit Kumar[1,3], Angela Xie[1], Richard Lock[1], Karen MacKenzie[1], Paul Ekert[1,4], Andrew Fellowes[3], David Ziegler[1,2], Toby Trahair[1,2]

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~1000 children in Australia are diagnosed with cancer each year, among the highest incidence internationally (Baade et al., 2010, *BrJ Cancer*), and cancer remains the leading cause of death by disease in children. Most cancer chemotherapeutics used to treat childhood cancers have non-specific cytotoxicity to both normal and cancer cells, resulting in significant health care costs (20–25% of the work in children's hospitals in Australia). 30% of survivors will suffer one or more serious life-altering health conditions as a result of the toxicity of current treatments (http://curesearch.org/Childhood-Cancer-Statistics). A personalized medicine trial is being undertaken to assess the feasibility of a diagnostic platform for the identification of novel therapeutic agents for high-risk pediatric malignancies with expected overall survival ≤30%. Patients' tumor and germline samples are being collected at diagnosis and/or relapse and analyzed using: (1) Genetic analysis (targeted molecular profiling [DNA, RNA], WGS, RNASeq); (2) In vitro high throughput drug sensitivity screening; (3) In vivo drug response testing using patient derived xenograft models. Since the launch of the feasibility study, 24 children have been enrolled, and where sufficient and appropriate tissue samples have been available, methods described above have been performed, and results combined and correlated with clinical data. The proportion of patients where results inform an alteration of treatment leading to improved clinical outcome will be assessed. This study may provide the evidence that personalized cancer therapy has the potential to improve outcome and reduce treatment-related toxicities, and hence reduce the burden to the health care system.

2. WITHDRAWN

3. IS CONSECUTIVE MISMATCH REPAIR (MMR) GENE GERMLINE MUTATION TESTING ASSOCIATED WITH AN INCREASE DETECTION OF MMR GENE MUTATIONS IN THE DIAGNOSIS OF LYNCH SYNDROME IN PATIENTS WITH COLORECTAL CANCER?

Megan Higgins[1], Jan Wakeling[1], Rachel Susman[1], Helen Mar Fan[1]

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Background: Lynch syndrome (LS) is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes, leading to an increased risk of cancer, including colorectal cancer (CRC). Immunohistochemistry (IHC) on tumor tissue to detect loss of MMR protein expression is used to screen for individuals at risk of LS. Current guidelines suggest that germline mutation testing should be based on the IHC pattern of MMR protein loss and that testing of the second relevant MMR gene be performed if the first is uninformative. Results of a study undertaken at Genetic Health Queensland (GHQ) on germline mutation analysis on women with IHC loss of MMR protein expression in endometrial tumor tissue are also being presented (see abstract by Znaczko et al). *Aim:* To determine if consecutive germline mutation testing is associated with increased detection of MMR gene mutations in patients with CRC. *Methods:* We performed a retrospective analysis on patients who attended GHQ between 2000–2016 and had consecutive MMR germline mutation testing based on CRC tumor IHC +/- BRAF testing. Data analyzed included age of diagnosis, IHC results, family history and MMR gene test results. *Results:* The results will be presented and will include the number and proportion of MMR gene mutations found on the second MMR gene test and whether this is associated with a significantly increased rate of mutation detection. We will discuss how the results impact on clinical practice and utility of performing a second germline mutation test to improve the diagnostic yield in LS.

4. A PROSPECTIVE SURVEILLANCE STUDY FOR GERMLINE TP53 VARIANT CARRIERS UTILIZING WHOLE BODY MRI

Mandy Ballinger[1], Sue Shanley[2], Paul James[2], Alison Trainer[2], Gillian Mitchell[2], Nicholas Ferris[3], Kate Moodie[2], Marion Harris[3], Kate McBride[4], Mary-Anne Young[2], David Thomas[1]

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Background: TP53 pathogenic variant carriers ascertained on family history have an extremely high lifetime cancer risk. As costs

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decrease making sequencing more available, more TP53 variant carriers are being identified in non-traditional settings. Comprehensive cancer risk management guidelines for this population are lacking. *Aims:* To estimate the prevalence and incidence of investigable lesions in this high-risk population and assess the acceptability, psychosocial impact and cost effectiveness of the surveillance program. *Methods:* The surveillance program includes annual whole-body MRI, clinical review and physical examination, full blood evaluation, fecal occult blood testing (FOBT), breast MRI and 2–5 yearly colonoscopy/endoscopy. Psychosocial evaluations are undertaken and participants complete cost diaries. Medicare/PBS data will also be extracted. *Results:* Since July 2013, 25 TP53 pathogenic variant carriers (15F, 10M; age 18–63 years) have been enrolled. After completion of 25 first-year whole body MRI scans, 9 individuals have required further investigations (1 chest CT, 1 thallium scan, 4 US, 3 MRI/US and biopsy, 3 targeted MRI). Two new asymptomatic malignancies (well differentiated liposarcoma and a Gleason score 8 prostate cancer) have been detected as well as a recurrent leiomyosarcoma. All blood evaluations and other screening procedures (9 colonoscopy, 6 endoscopy, 16 FOBT, 7 breast MRI) have been normal. Preliminary psychosocial data indicate no lasting adverse effects. *Conclusion:* Evaluation of the surveillance schedule is in the early stages. The detection of two asymptomatic primary malignancies (treated with curative intent), in conjunction with the acceptability and lack of negative psychological impact supports continuation for a longer term.

5. OUTCOME OF GENETIC TESTING OF MLH1, PMS2, MSH2 AND MSH6 GENES BASED ON IMMUNOHISTOCHEMISTRY MISMATCH REPAIR (IHC MMR) STAINING IN WOMEN DIAGNOSED WITH ENDOMETRIAL CANCER

Anna Znaczko, Goutham Sivasuthan, Jan Wakeling, Rachel Susman, Helen Mar Fan
Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Background: Lynch syndrome (LS) predisposes patients to cancer, including endometrial cancer (EC). Women with LS have an estimated lifetime risk of 42% to 60% for developing endometrial cancer. LS is caused by a mutation in one of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6 or PMS2). Immunohistochemistry (IHC) performed on tumor tissue to detect loss of MMR protein expression is used to screen for individuals at risk of LS. MMR proteins form dimers (MLH1 with PMS2 and MSH2 with MSH6). It has been local practice to test the second gene from the dimer pair when initial gene testing is uninformative (e.g. MSH2 gene testing followed by MSH6 where there is loss of MSH2 and MSH6 proteins on IHC). *Aim:* To identify the proportion of MMR gene mutations detected in patients diagnosed with endometrial cancer whose cancer tissue showed loss of MMR protein expression. *Methods:* We identified 77 patient diagnosed with endometrial cancer whose cancer tissue showed loss of MMR proteins. We performed a retrospective data analysis of the mutation detection rate in the first MMR gene and, if undertaken, the second MMR gene. Data analyzed included age, personal and family history of cancer, IHC results, first MMR and second MMR gene testing result. *Discussion:* We have not identified any mutations in the PMS2 gene where there was loss of expression of MLH1 +/- PMS2 and MLH1 germline testing was negative. A similar conclusion applied to MSH6 testing where there was loss of expression of MSH2 +/- MSH6.

6. EVALUATING THE PERFORMANCE OF THE TRUSIGHT TUMOR PANEL FOR SOMATIC MUTATION TESTING OF FFPE SPECIMENS

David Fairbairn[1], Kristina Goodwin[1]
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The TruSight Tumour (Illumina) NGS methodology was introduced to increase the range of somatic mutations detected and facilitate simultaneous testing of multiple oncogenes in formalin fixed paraffin embedded (FFPE) specimens. For this type of specimen, tissue availability can be limited, which results in low yields of DNA that is often of poor quality, fragmented and chemically modified. Furthermore, the range of somatic cancer mutations that confer sensitivity or resistance to an associated target therapy is expanding. The previous approach of screening individual genes, rather than multiple genes in parallel, cannot be performed when minimal specimen is available. The TruSight Tumour 26 (TST26) panel was introduced into regular routine diagnostic testing for somatic mutations in cancer. The method was validated against 96 DNA samples from previously tested patient samples and commercial reference standards. The performance of the method was monitored during the first 6 months of operation. The results from over 800 patients were used to redefine the analysis parameters and quality acceptance criteria. Details of the results, operational issues encountered and an analysis of the mutations detected are presented.

7. TESTING FOR FAMILIAL ADENOMATOUS POLYPOSIS AND MYH-ASSOCIATED POLYPOSIS: HOW LOW CAN YOU GO?

Kirsty Storey[1], Lindy Hodgkin[1], Jessica Taylor[1], Finlay Macrae[1,2,3]
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[3]*Department of Medicine, University of Melbourne, Melbourne, VIC, Australia*

Classic familial adenomatous polyposis (FAP) is characterized by hundreds of adenomatous polyps. MYH-Associated Polyposis (MAP) accounts for a subset of patients with adenomatous polyposis. APC and/or MYH genetic testing for these conditions is well accepted in a young person with greater than 20 adenomatous polyps. However, there is less consensus for testing when polyp numbers are between 10–20 and whether an age limit should be applied. Genetic testing criteria for polyposis conditions provide a guideline to the genetics service and to clinicians about when to refer to a Familial Cancer Centre. As panel tests become the standard of care, it is even more important that testing guidelines are evidence-based and cost-effective. The National Comprehensive Cancer Network advocates for testing patients with more than 20 adenomas and 10–20 polyps, upon meeting other criteria. EviQ guidelines promote APC testing in patients with at least 20 adenomas, or at least 10 adenomas and if under age 30. EviQ guidelines for MYH testing are currently under review. The Royal Melbourne Hospital Familial Cancer Centre has an internal policy of testing patients with at least 10 adenomas. We audited the 161 patients tested in the last 5 years to assess the detection rate of APC and MYH mutations according to number of adenomas and age of polyposis onset. Preliminary results suggest that patients tested for at least 10 or more adenomas under the age of 60, yields detection rate of over 10%. Results of this audit, in addition to existing guidelines, will shape future practice.

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8. FEELING OVERWHELMED BY BOWEL/UTERINE CANCER REFERRALS? HOW ABOUT TRYING THIS STREAMLINED AND COST-SAVING APPROACH!

Emily Higgs[1], Lindy Hodgkin[1], Catherine Beard[1], Michael Bogwitz[1], Kirsty Storey[1], Jessica Taylor[1], Maira Kentwell[1,2], Stephanie Badman[1], Adrienne Sexton[1], Emma Creed[1,3], Alana Druitt[1,4], Paul A James[1,5], Alison Trainer[1,5], Finlay Macrae[1,6]

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The Royal Melbourne Hospital Familial Cancer Centre has developed a triaging process for bowel/uterine cancer referrals to increase efficiency of service delivery. We will present this process (including an interactive component), which is designed to stratify families into low/moderate/high hereditary risk categories to ensure clinical service time is focussed on high risk families. Personal and family cancer history and individual histopathology are used for preliminary assessment. The key features of this triage process are: (1) Testing of MLH1 promoter methylation is ordered during intake for patients with known loss of expression of MLH1/PMS2 proteins in their bowel/uterine tumor, saving preliminary appointments where methylation testing would have been arranged. Patients with methylation detected in their tumor are discharged (by phone and letter) where the abnormal immunohistochemistry (IHC) was the only high risk feature. (2) A subset of patients is preliminarily assessed as low/moderate hereditary risk. Where IHC analysis of a family member's tumor could change the assessment to high risk, patients are discharged back to the care of their referring doctor using a standard letter with the option of the family pursuing IHC testing then reassessment. This process is genetic counselor and intake assistant-led, with clinician input before discharge. we will present an audit of the outcomes of this streamlined process. We propose this will significantly improve time and cost efficiencies, provide consistent clinical care, and promote education of referring doctors. In future, we hope this process will be collaborative with referring health professionals, in moving towards a mainstream approach.

9. A COLLABORATIVE APPROACH FOR IDENTIFYING BRCA1/2 MUTATIONS IN FAMILIES WITHOUT A LIVING CANCER AFFECTED FAMILY MEMBER

Jennifer Berkman[1], Jan Wakeling[1], Julie McGaughran[1]

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Mutations in the BRCA1 and BRCA2 genes confer a high risk of breast (50–60%) and ovarian (20–40%) cancer in women, and increased breast and prostate cancer risks in men. Offspring of mutation carriers have a 50% chance of inheriting these mutations. Currently, predictive testing in unaffected individuals can only be offered when a mutation is known in the family. For most families in which no affected family member has been tested, and there is no living cancer affected family member, BRCA1/2 gene testing and the associated health benefits are unavailable through the public health system. A lack of testing can result in unnecessary cases of advanced cancer with significant morbidity, mortality and healthcare costs. The chance of finding a mutation increases with the number of tested individuals at 50% risk of inheriting a gene fault, if present in the family. For groups of three or four DNA samples the chance of detecting the mutation (if present) is 87.5% or 94%, respectively. The aim of this project was to develop a protocol for testing unaffected family members for BRCA1/2 mutations when no affected family member is available. Six families were recruited with 20 BRCA1/2 mutation tests offered by NGS. One BRCA1 mutation was detected in an individual who had never sought testing, allowing cascade screening in relatives. This result demonstrates the utility of a collaborative approach to test multiple unaffected at-risk relatives in order to find a causative mutation. This approach will become increasingly viable as the cost of NGS decreases.

10. 'THE RESULT IS A LITTLE MORE COMPLICATED THAN WE EXPECTED': AN INCIDENTAL FINDING IN BRCA PREDICTIVE TESTING

Rachel Pope-Couston[1], Kimberley Gamet[1], Phillipa Dryland[2]

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Introduction: Often, genetic counseling for predictive testing may not focus on the possibility of incidental or unexpected findings due to the perception that the narrow focus of genetic testing for known mutations would make those types of findings highly unlikely. In this case, due to the nature of the test platform being used, it was found that while the consultant did not carry the maternal familial BRCA1 deletion, he did carry a pathogenic duplication. This incidental finding was a novel experience for both the genetic counselors and laboratory staff involved and required management of a number of complex issues. *Methods:* Laboratory staff liaised with the genetics unit to develop a report which accurately reflected how the finding had been detected. Counselors involved considered a number of ethical issues in preparation for providing the result to the consultant and working with his family. These included planning how, or if, to raise the possibility of non-paternity given the low de novo rate for BRCA mutations and the absence of a reported paternal family history of cancer. *Outcome:* Collaborative communication between the laboratory and genetic counseling staff and between genetic counselors and family members was the key to effectively managing this incidental finding and the flow-on effects within the family. Successful communication and support has resulted in a number of at-risk relatives coming forward for predictive testing. This case also highlighted the importance of comprehensive pre- and post-test counseling, particularly as the resolution and complexity of genetic testing platforms continues to increase.

11. EVALUATION OF A TAMOXIFEN INFORMATION GUIDE FOR WOMEN AT MODERATE TO HIGH BREAST CANCER RISK

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[6]*Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Tamoxifen has been proven to reduce breast cancer risk by 38% (95% CI 28–46%) in women with a moderate to strong family history; however, uptake of the therapy remains relatively low. Women have indicated that they require additional information about tamoxifen before making an informed choice regarding their treatment. Due to the lack of appropriate information available regarding tamoxifen, a new resource has been developed to meet the needs of these women. *Aim:* To evaluate the usefulness of a leaflet designed to inform women about the risks and benefits associated with taking tamoxifen to reduce their breast cancer risk. *Methods:*

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The leaflet has been designed to provide balanced information on the risks and benefits associated with taking tamoxifen to reduce breast cancer risk. It has been tailored to an 8th grade reading level, to ensure that the information is accessible to the target audience. Participants ($N = 30$) will be recruited on the basis of having a moderate to high breast cancer risk. After consulting with their clinician about risk-reducing options, participants will be provided with a leaflet about tamoxifen. Participants will then be asked to provide feedback on: layout; depth and appropriateness of information provided; and whether or not the leaflet was presented and worded in a way that was easy to understand. Responses will be analyzed using descriptive statistics for these measures. *Results/Conclusion:* Modifications will be made to the leaflet based on pilot results prior to dissemination to familial cancer clinics, which will provide the resource to patients.

12. EXPLORING THE BARRIERS IMPACTING UPTAKE OF FAMILIAL CANCER SERVICES WITHIN ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITIES OF THE PEEL SECTOR OF HUNTER NEW ENGLAND LOCAL HEALTH DISTRICT

Rebecca Harris[1], Rachel Williams[2], Kristine Barlow-Stewart[1], Jane Fleming[1], Melissa Buckman[3]

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Hereditary cancers account for up to 10% of all cancer diagnoses, and, therefore, there is benefit in determining an individual's inherited risk, before cancer occurs. Within Australia, genetic services provide an assessment of family history of cancer. Anecdotally it has been noted that the number of clients referred to genetic services in the Peel Sector of the Hunter New England Local Health District (HNELHD), to discuss family history of cancer, does not reflect the Aboriginal population in the area. Traditional holistic health models, in which spiritual, mental, cultural, emotional and social connections are all inclusive, are still practiced by Aboriginal communities around Australia. However, there is no information available to suggest how these cultural influences and understanding of health and wellness influences the motivation of clients in seeking familial cancer services. This paper will discuss the process of conducting research with an Indigenous community and our progress in proposing a series of 'yarns' with Aboriginal Elder community members. Important concepts of exploration will focus on keeping the family healthy and well. Topics of discussion will include the understanding of the causation of cancer, known experiences of cancer in families and the community, feelings associated with having a family history of cancer, perceptions of cancer and the experience of seeking and utilizing healthcare. Results from this study will be used to provide culturally appropriate care to the community, support the principles of the 'Closing the Gap' policy, and to create a functional partnership between genetic services and local Aboriginal Medical Services.

13. REACHING A DIAGNOSIS OF LYNCH SYNDROME IN AN OLDER WOMAN WITH LIMITED FAMILY HISTORY: THE IMPORTANCE OF EFFECTIVE LIAISON BETWEEN THE GENETICS AND PATHOLOGY SERVICES

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Working within clinical genetics, it is essential to be able to liaise effectively with colleagues in related services to achieve optimal outcomes for our patients. A case is presented here which highlights how effective synthesis of the pertinent information and effective communication with our colleagues in pathology helped to achieve an informative outcome for our patient. Jane, a 72-year-old woman, was referred to Genetic Health Queensland after being diagnosed with a with a rectosigmoid adenocarcinoma. Initial analysis of this tumor demonstrated retained expression of MLH1 and MSH2, loss of expression of PMS2 and patchy loss of MSH6. A query of Lynch syndrome was raised. Jane was an only child and the family history was uninformative. To try to clarify the MMR protein expression results, immunohistochemical analysis of the biopsy sample was requested and inconsistent results were obtained. Significant liaison between the relevant pathology services and the genetics service ensued. The final assessment was that the tumor exhibited loss of expression of PMS2, with the patchy loss of MSH6 reflecting a secondary event. Genetic testing of PMS2 was undertaken and an unclassified variant identified. A second blood sample to enable RNA analysis was provided. Pathogenicity of the variant was still unclear. A summary of the clinical history for this patient was provided and the details of the variant were discussed at a specialist classification meeting. The variant was assessed as pathogenic. This confirmed the diagnosis of Lynch syndrome in our patient and will enable predictive testing for other family members.

14. TWO FAMILIES WITH LYNCH SYNDROME AND ADRENOCORTICAL, PROSTATE AND MEDULLARY THYROID MALIGNANCIES WITH ABSENT MISMATCH REPAIR PROTEIN STAINING

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Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, predisposes to a number of cancers with colorectal and endometrial cancer being the most common. While a strong association with colorectal and endometrial cancer has been well documented, it remains somewhat controversial which other cancers are part of the LS spectrum. We report two interesting cases of LS; the first, secondary to an MSH2 mutation in which absent MSH2 staining was identified in several sebaceous adenocarcinomas, adrenocortical and prostate carcinomas in two brothers both carrying the MSH2 mutation and the second due to an MSH6 mutation where the proband had loss of MSH6 staining in a medullary thyroid carcinoma in addition to CRC. These unusual examples of absent mismatch repair protein staining in individuals with LS suggest that immunohistochemistry in tumors outside of the LS spectrum may be useful in identifying cancers associated with an underlying germline mutation.

15. FURTHER EVIDENCE FOR POLE AS A PREDISPOSITION GENE IN LYNCH SYNDROME

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Background: Genetic susceptibility accounts for up to 35% of colorectal cancer (CRC) predisposition; high penetrance germline mutations in known CRC-susceptibility genes are found in 3–5% of all CRC. High risk genes include the DNA mismatch repair genes,

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APC, MUTYH, STK11, BMPR1A, SMAD4, PTEN and more recently, the POLE and POLD1 genes. Lynch syndrome in an autosomal dominant inherited cancer susceptibility syndrome, where carriers of mutations in the mismatch repair genes are predisposed to cancers especially of the colorectum and endometrium. The POLE c.1270C>G, p.(Leu424Val) mutation has been emerged as a low frequency but highly penetrant variant in familial CRC and polyposis patients, explaining approximately 0.25-1.4% of the heritability in CRC. *Case study and Conclusion:* We report a novel POLE variant c.1708C>A p.(Leu570Met) in a 28 year old man with suspected Lynch syndrome. Individual testing for this gene may not be cost effective. With the transition from genetics to genomics, with multigene testing panels and whole exome sequencing, inclusion of this gene in the investigation of the heritability of CRC is warranted. Given the evident phenotype, with its similarity to LS, consideration of risk management colonoscopic surveillance as for LS seems prudent, as more data is gathered about the clinical utility of mutations in this gene.

16. PROVIDING ANSWERS FOR HNPCC FAMILIES: FROM RESEARCH TO CLINICAL TESTING

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Current screening methodology for hereditary nonpolyposis colorectal cancer (HNPCC) at Pathology North, (Newcastle) involves sequencing of the intron/exon boundaries of the MLH1, MSH2 and MSH6 genes and Multiplex Ligation-dependent Probe Amplification (MLPA). This is sufficient for most families; however there are a considerable number of families with a typical phenotype of Lynch syndrome but with no mutation found. Recent evidence suggests there are more cryptic mutations occurring within regions of MSH2 that are not amenable to detection using standard strategies. A number of requests from clinicians to confirm research findings and subsequent literature review has resulted in Pathology North incorporating three new tests into its MSH2 screening protocol. The MSH2 Supplementary Panel includes screening for a 10Mb inversion of exons 1–7, an inversion of exons 2–6 and a deep intronic change, c.212-478T>G. The inversions are detected with a PCR utilizing break-point specific primers while the deep intronic change has been detected by DNA sequencing. This panel has been incorporated into all new probands from 1st February 2016 or can be specifically requested for patients previously screened for MSH2. We currently have a number of probands who have been found to carry one of these mutations. The majority of these probands had been tested for MSH2 mutations in the past and a few have been in the system for quite some time. This is a valuable demonstration on how new strategies developed in the research laboratory can be translated to clinical practice in order to provide resolution for HNPCC families.

17. AN INTERESTING CASE OF TP53 MOSAICISM RAISES ISSUES FOR GENOMIC GENETIC COUNSELING

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We present an interesting case of Li Fraumeni syndrome (LFS). Mary was referred to Genetic Services of Western Australia (GSWA) in 2014, following her diagnosis of breast cancer at the age of 29. At that time the only other known family history of possible significance was Mary's late father's diagnosis of NHL at 56. BRCA and TP53 diagnostic testing of Mary was inconclusive: (1) BRCA1 and BRCA2: MPS and MLPA (gDNA); (2) TP53: Sanger sequencing and MLPA (cDNA). In 2016, Mary's daughter was referred to GSWA following a diagnosis of metastatic bowel cancer at the age of 14. LFS was reconsidered and Mary's original sample was re-tested via MPS. A class 3 VUS (c.418A>T) was identified by MPS, and confirmed by Sanger sequencing, which in turn identified mosaicism for the VUS and a pathogenic deletion (c.390_426del). Mary's daughter was heterozygous for the deletion. This case is currently in the process of being investigated further, but the information that is currently available raises a number of issues that are of relevance to those involved with the integration of genomics into healthcare. These include: (1) unidentified mosaicism as an alternative explanation for inconclusive testing; (2) advantages, limitations and complexities of different diagnostic testing techniques; (3) possible mechanism for de novo TP53 deletion; (4) importance of variant classification; (5) communication of discrepant and complex results to patients; (6) importance of effective communication between clinical and laboratory genetic colleagues. Additional details will be available by the time of the HGSA Annual Scientific Meeting.

18. WITHDRAWN

19. CONTINUING TO MANAGE 'THE ANGELINA JOLIE EFFECT': A NEW INTAKE PROCESS

Stephanie Badman[1], Jessica Taylor[1], Kirsty Storey[1], Maira Kentwell[1], Catherine Beard[1], Emily Higgs[1], Melanie O'Loughlin[2], Alison Trainer[1,2], Paul James[1,2], Finlay Macrae[1,3], Geoffrey Lindeman[1,4]
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Background: Angelina Jolie's disclosure of her BRCA1 mutation carrier status in May 2013 was followed by a period of intense media interest and more than doubling of Familial Cancer Centre (FCC) referrals (James et al MJA 2013, 99:646). This prompted a modification of the intake process at The Royal Melbourne Hospital (RMH) and Peter MacCallum (PM) FCCs, with the aim of managing increased workload. Following the lead of the South Australian Clinical Genetics Service, the FCCs trialled sending standard letters to the referring doctor, in response to low and moderate risk referrals. *Aim:* To conduct a clinical audit of referral outcomes arising from the modified intake process. *Results:* In the 2014 RMH data subset, 266 referrals were reviewed that did not meet the high risk category at intake; 35%($n = 94$) were sent a low or moderate risk discharge letter, 27%($n = 71$) were sent a request for more information, 24%($n = 63$) were managed as high risk referrals, and 14%($n = 38$) resulted in other miscellaneous contact. Where a request for more family history information was made, 33%($n = 23$) responded and 24%($n = 17$) were then redirected to the high risk pathway. Overall, 55%($n = 147$) of referrals reviewed were discharged using standard letters. Analysis of the PM data set is pending. *Conclusion:* This system has provided a reliable and efficient way of managing an increase in workload, by streamlining triage of referrals to improve the identification of high risk families. This updated intake process also provided an opportunity to educate non-genetics health professionals, as clinical genetics moves into the mainstream setting.

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GENETIC COUNSELING

20. WITHDRAWN

21. NEUROFIBROMATOSIS TYPE 1: THE NEXUS BETWEEN GENERAL AND CANCER GENETIC COUNSELING

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Neurofibromatosis type 1 (NF1) is an autosomal dominant condition, with an incidence of around 1 in 5,000. Features of NF1 can include multiple neurofibromas visible on the skin, café au lait macules, scoliosis, mild learning disability, high blood pressure, as well as optic nerve pathway and brainstem gliomas, breast cancer and pheochromocytoma. Whilse NF1 is highly penetrant, it displays variable expression. Around 50% of NF1 cases are the result of a de novo mutation. Because NF1 can present with benign and cancerous tumors, as well as features affecting an individual's quality of life, genetic counseling for NF1 requires counseling skills utilized in both general and cancer genetic settings. The genetic counseling challenges encountered in NF1 cases are compounded by the condition's variable expression, with some families experiencing an unusually heightened penetrance of cancer, compared with mutation positive individuals who don't meet clinical criteria for a diagnosis of NF1. We have used three NF1 cases to highlight these genetic counseling challenges, which include grief and loss, the emotionally charged question 'why me?', cancer anxiety, guilt over the limited expression of NF1 in a mother compared to her more severely affected children, the experience of a diagnostic odyssey and the impact of NF1 on quality of life.

22. THE IMPACT OF GENOMICS ON GENETIC COUNSELING: AN EXPLORATION OF AUSTRALIAN STAKEHOLDER VIEWS

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There is agreement among clinicians and healthcare providers that genomic technology — specifically in the context of sequencing large panels of genes or whole genomes — will have a wide impact on many health professionals, particularly genetic counselors. While there has been much debate about the impacts of genomics on genetic counseling in Europe and the United States, there has been little exploration of professional views in Australia. This study aimed to characterise the similarities and differences between a genetic and a genomic counseling session, and answer the following questions: What should genomic counseling involve? Is it adapted from, or a significant departure from genetic counseling? What training is required for genetic counselors in the genomic era? Seventeen genetic counselors and clinical geneticists/medical specialists agreed to participate (RR = 53%) in semi-structured telephone interviews, based around five hypothetical scenarios that encompassed potential clinical challenges associated with genomic testing. Interviews were transcribed, de-identified coded and analyzed for salient themes. Several key themes emerged throughout these interviews including the importance of tailored pre-test counseling, differences between genetic and genomic counseling, the role of the genetic counselor in genomic testing, challenges in reporting genomic results, and requirements for staffing and training of genetics professionals. These results are informing discussions of frameworks to guide genetics professionals transitioning into the genomic era.

23. UNDERSTANDING THE VALUE OF A GENETIC DIAGNOSIS BY NEXT GENERATION SEQUENCING FOR AUSTRALIANS AFFECTED BY CONGENITAL CATARACT

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While new sequencing techniques have increased the identification of disease causing mutations, next generation sequencing (NGS) is also associated with challenges, which have considerable implications for patients and their families. Understanding the impact of a genetic diagnosis for families is therefore important to inform the introduction of NGS testing to clinical practice. The use of NGS has been described for multiple conditions; however, little research has focused on developmental eye diseases and none have focused on congenital cataract (CC) to date. CC is a highly heterogeneous developmental eye disease characterized by cataract formation at birth or in early childhood, and there are syndromic forms. This condition is clinically and genetically complex with a poor genotype-phenotype correlation. Although NGS now offers improved identification of previously undetected causative mutations for CC, the perceived value of a genetic diagnosis by NGS is poorly documented for this population group. This qualitative study is exploring the perceived value of NGS for a cohort of parents whose child(ren) had mutations identified by targeted exome sequencing for apparently non-syndromic CC. The patient cohort has been identified for recruitment and purposive sampling is underway to identify potential participants. Semi-structured interview questions have been designed to explore parents' experiences of NGS and its impact on their families. De-identified transcripts from the interviews will be analyzed thematically using an inductive approach. Themes identified in this study will inform best practice in support of families undertaking NGS for genetic diagnosis of CC in the clinic.

24. VARIANT PATHOGENICITY ASSESSMENT IN CARDIAC GENETIC TESTING

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Aim: Genetic testing for cardiac disorders renowned for their complex genetic pathology is quite challenging for the laboratory when it comes to interpretation of findings and determining whether a variant is pathogenic, likely to influence clinical severity or is benign. The outcome of testing and result interpretation is of utmost importance to clinical management. *Method:* Our lab uses a custom Next Generation Sequencing gene panel to screen patients with cardiomyopathies, arrhythmias, aortopathies and congenital heart disease. Data analysis occurs through a custom pipeline and the complete coding sequences of all genes are screened and all variants with population database frequency <1% are reported. *Results:* Variant classification is constantly evolving due to new information in 'normal' populations or new reports of the variant being associated with disease. We have developed curation guidelines which include subcategorization of variants of unknown significance into: high clinical signifance, unknown or low clinical significance. We recommend variants of high clinical significance are segregated in family members in order to further clarify their association with disease. An initial biological classification assesses the variant in the context of its impact on the gene protein and published evidence of

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clinical impact. *Conclusion:* Assessing the variant in the context of other variants identified, evidence of clinical impact and the presence or absence of variants in other family members facilitates a clinical classification specific for the family. The clinical classification has contrasted the biological classification in some cases, emphasizing the importance of this type of assessment within a clinical application.

25. EXPLORING ADHERENCE TO MEDICAL GUIDELINES AND QUALITY OF LIFE FOR AUSTRALIANS WITH DUCHENNE MUSCULAR DYSTROPHY

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Introduction: Duchenne muscular dystrophy (DMD) is a common disorder resulting in mortality in early adulthood. Improvements in healthcare have transformed the natural history of this disorder. The study aim was to characterise the Australian care experience and adherence to current guidelines and self-reported quality of life (QoL) for men with DMD in Australia. *Methods:* As part of a larger study ($n = 142$), men (>18years) with DMD were recruited through the national DMD registry and neuromuscular clinics across Australia. Participants completed the international CARE-NMD questionnaire (42 question self-report survey) and QoL measures (WHOQOL-BREF and SF-36). *Results:* We recruited 29 men (mean 25.6 yrs ± 6.6). Half (58%) of the participants were unemployed and not undergoing higher education. Most adults live at home with their families, with only 2 individuals residing on their own. Of the respondents over a third attended a specialist clinic less than yearly or not at all. Over half (58%) of the participants received an echocardiogram at least once per year and 48% had respiratory assessments at least once per year. Only the physical domains declined with age on the WHOQOL-BREF ($r = -.39$, $p = .01$). However, all domains on both measures were below that of normative samples. *Conclusion:* Preliminary results suggest most care received by adults with DMD aligns with current medical guidelines. However, medical teams need to inform their patients about best practice to improve self-directed care. Social functioning was below average so interventions targeting increased engagement in the community would be of benefit for enhanced QoL.

26. ESTABLISHING A NEW MULTIDISCIPLINARY NEUROFIBROMATOSIS CLINIC

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Due to the multisystemic nature of Neurofibromatosis (NF), multidisciplinary NF clinics exist across the developed world. Such services are limited in Australasia, and many children with NF are reportedly lost to follow up. The Royal Children's Hospital NF Clinic was established in 2015, with the Victorian Clinical Genetics Services, to provide diagnosis and management for children with a suspected or clinical diagnosis of NF. The clinic team comprises specialists in neurology, genetics, genetic counseling, plastic surgery, neuropsychology, ophthalmology and transition services. An NF Registry is being established to facilitate further education and research. When new multidisciplinary clinics are established for genetic conditions, the onus of clinic development and maintenance often falls to genetic counselors. In this case, an iterative process was applied to determine appropriate clinic setup and procedures. Later integration of an 'NF Support Coordinator' into the clinic enabled comprehensive case management beyond the scope of the clinic's existing genetic counselor. Employing a genetic counselor in this new role proved invaluable. A longitudinal evaluation of clinical outcomes is currently underway. Plans are also in place to develop partnerships with adult services for adolescent transition to these services. We describe our experience of establishing and coordinating a multidisciplinary neurofibromatosis clinic; discussing considerations and challenges encountered. Patient demographics, referral paths and coordination of care during the first 18 months of the clinic will be presented. Lessons learnt from the process may assist genetic counselors and other health professionals setting up multidisciplinary clinics.

27. FXTAS IN INDIVIDUALS WITH FRAGILE X FULL MUTATION

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Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability. FXS is characterized by a CGG expansion of more than 200 repeats (full mutation) in the fragile X mental retardation 1 (FMR1) gene, which usually results in the gene becoming methylated and silenced. Fragile X associated tremor ataxia syndrome (FXTAS) is commonly recognized as a late onset neurodegenerative disorder affecting premutation carriers with CGG repeat expansions between 55–199. FXTAS affects approximately 40% of male carriers and 8–16% of female carriers.

We will present two FXS cases, one male aged 33 years and the other 38 years seen by the GOLD Service (Genetics of Learning Disability) presenting with clinical and MRI features consistent with FXTAS. We will describe our follow-up of these patients beyond the standard genetic testing to explain their presentation of FXS and FXTAS, their experiences and management. These two cases highlight: (1) limitations of standard genetic testing; and (2) that there is much to be learned about late onset disorders in FXS patients.

28. AN EVALUATION OF THE GENETIC SUPPORT NETWORK OF VICTORIA: A MIXED METHOD PARTICIPATORY APPROACH

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Background: Individuals affected by genetic and rare conditions have unique support and health care needs. Supportive services seeking to provide appropriate and accessible help must first understand the needs of these individuals within a rapidly developing genetics health environment. *Aims:* This study aims to investigate the support needs of individuals who had previously accessed

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the Genetics Support Network of Victoria (GSNV) and explore their beliefs and attitudes toward the network. Taking a participatory evaluation approach, the views of stakeholders and GSNV staff members were additionally explored to uncover avenues for organizational improvement. *Methods:* Participants were GSNV service users who had accessed the service within the past 12 months (e.g., individuals affected by genetic and rare disease, health professionals and support group organisers), representatives from key stakeholder groups and GSNV staff members ($n = 40$). Five focus groups were conducted with participants grouped together based on their relationship to the GSNV. Adopting a phenomenological approach, the focus group discussions were transcribed verbatim and coded using thematic analysis to identify major themes. *Results:* Preliminary data in this study will elucidate important themes across the group discussions related to participants' experiences seeking support from the GSNV, beliefs and attitudes towards the network, unmet information and support needs and ideas for organizational growth and change. *Conclusion:* This research provides insight into the experiences of members of the genetics health community, including their help-seeking behaviors. The findings may enhance the appropriateness and utility of GSNV services and inform the development of genetic support structures elsewhere in Australia.

29. GENOMIC COUNSELING FOR GENETIC COUNSELORS — REPORT AND EVALUATION OF THE INAUGURAL NSW WORKSHOP

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Background: The advent of the genomic era has paved the way for the implementation of whole exome sequencing (WES) and whole genome sequencing (WGS) into clinical practice. The complexity of these technologies presents challenges that may require new or modified genetic counseling strategies. Anecdotally, genetic counselors in NSW report a growing concern and need to upskill in genomics. *Method:* Genetic counselors from the Department of Medical Genomics, Royal Prince Alfred Hospital, with support from the Garvan Institute of Medical Research and the Centre for Genetics Education conducted a 2-day workshop, 'GC4GCs', in October 2015. Key experts in clinical genetics, ethics and bioinformatics contributed. The program included a 'variant calling' practical workshop and panel discussion on the evolving role of genetic counselors. The workshop was exclusively for practicing genetic counselors invited via GC List Serv. Evaluation involved a post-workshop questionnaire. *Results:* Sixty-two participants completed the evaluation; the majority of participants had >5 years clinical experience. The workshop was overwhelmingly well received by participants, with 97% responding positively. Participants reported that the program covered topics of interest at an appropriate level, filling a gap in knowledge. The high quality of speakers was noted. Participants would have liked a longer session for 'variant calling', more practical examples and the role of genetic counselors explored further. There was a call for more workshops in the future, particularly once genomic testing becomes more readily available. *Conclusion:* Evaluation of the workshop highlighted a clear need for professional development opportunities in genomics among practicing genetic counselors.

30. ONGOING NEEDS OF ADULTS WITH GENETICALLY CONFIRMED NEUROMUSCULAR AND/OR COGNITIVE CONDITIONS

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Background: We outline initial results of a gene carrier review program for a multidisciplinary Neurogenetics clinic. In 2015 there were 240 clinic appointments for clients with a range of neuromuscular and/or cognitive conditions such as amyotrophic lateral sclerosis, Huntington's disease, CADASIL, ataxia, hereditary spastic paraplegia and Charcot Marie Tooth disease. This clinic has traditionally had a diagnostic focus, but a lack of coordinated follow-up pathways for these clients, who have conditions with many psychosocial and medical impacts, has prompted this trial of a formalized review program. *Methods:* A mail-out was sent to 48 individuals with a confirmed genetic mutation, offering a review appointment with a genetic counselor. The mail out consisted of a single page form, offering an appointment face-to-face or by phone, and with a series of brief questions about the type of concerns and the communication of genetic information in the family. *Results:* Almost half responded (23 of 48) either by returning the form or by phoning the service. Of the respondents, 17 requested a review appointment. This equates to more than one third of gene carriers having unmet needs, indicating a benefit for routine follow-up in the service. *Discussion:* There are unique medical and psychosocial issues for people who have a genetically confirmed neurogenetic condition, which genetic counselors are well-placed to address within a multidisciplinary setting. Here we will analyze the contact notes for review appointments and present some of the main concerns for gene carriers.

31. EXPLORING THE EXPERIENCES OF PARENTS WHO INTENDED TO DISCLOSE USE OF PREIMPLANTATION GENETIC DIAGNOSIS TO THEIR CHILDREN

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Limited research has been conducted into how parents disclose conception by preimplantation genetic diagnosis (PGD) to their children. This study explored parent's experiences in decision making around if, how and when they disclosed conception by PGD to their children. Women who had PGD for single gene conditions (monogenic PGD), or preimplantation genetic screening (PGS) for chromosome abnormalities at two IVF centres in Melbourne, and who had indicated in a previous study that they had disclosed, or were intending to disclose conception by PGD, were invited to participate. In-depth semi-structured interviews were conducted and transcribed verbatim. Phenomenology and narrative analysis were employed as the methodological framework and analysis method respectively. Five monogenic PGD and five PGS participants were interviewed. Participants who underwent monogenic PGD placed a greater importance on the technology than women who underwent PGS. Key themes regarding intention to disclose among all participants were wanting to: maintain an open and honest relationship with their children, reduce stigma, and inform the child for medical reasons. Parents who had not yet disclosed wanted to protect their child from the information or could not recall the technology

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being used. Disclosure of PGD was generally early in the child's life, initiated by either the parents or the child, and was met with acceptance or indifference in children. Participants discussed a need for additional support and information when deciding how to disclose. Overall, participants felt confident with their disclosure experience, however, more support and educational resources are needed to facilitate disclosure.

32. ASSESSMENT OF GROUP GENETIC COUNSELING SESSIONS WITH PATIENTS REFERRED FOR PREIMPLANTATION GENETIC SCREENING (PGS)

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Increasing demand for genetic counseling regarding preimplantation genetic screening for chromosomal aneuploidy and workforce pressures necessitates the exploration for more efficient methods of providing this service. A pilot study was conducted to determine whether group genetic counseling is an effective method for education and decision support in the fertility treatment context. In this pilot study, group genetic counseling was offered to individuals and couples seeking genetic counseling for preimplantation chromosomal aneuploidy screening through an in vitro fertilization service prior to beginning in vitro fertilization treatment. Those that declined a group session were given the option of an individual genetic counseling appointment. Both cohorts were asked to complete an evaluation following their attendance. This was designed to assess their level of satisfaction, perceived advantages and disadvantages of session type, barriers to participation, and requested feedback and recommendations for improvement. Client acceptability, as well as impact on the service (e.g., booking appointments, follow-up requirements, etc.) were also considered. The results of this pilot study will be presented. Findings regarding the assessment of group genetic counseling as an alternative to individual sessions are expected to be generally applicable to genetic screening decisions and may serve as a model for other general clinical populations.

33. ATTITUDES OF SPERM, EGG AND EMBRYO DONORS AND RECIPIENTS TOWARD THE GENETIC INFORMATION AND SCREENING OF DONORS

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Background: Gamete and embryo donors undergo genetic screening procedures, the purpose is to maximise the health of donor-conceived offspring. Frequently these include family history, karyotype and carrier screening for certain genetic conditions. In the era of genomic medicine, extended genetic screening (e.g., next generation sequencing) may be offered to donors for the purpose of avoiding transmission of harmful genetic mutations. These tests may have an impact both on donors and recipients. *Aim:* To explore the attitudes of donors and recipients at Melbourne IVF toward the genetic screening of donors, with the intention of enabling health professionals to improve screening protocols, and to guide genetic counseling of donors and recipients. *Methods:* Semi-structured in-depth qualitative interviews were conducted with eleven recipients and nine donors from three different cohorts (sperm, egg and embryo) to explore the importance of the genetic information of donors and recipients. These were transcribed verbatim and thematic analysis was undertaken. *Results:* Donors understood the importance of genetic information; however the majority of donors were apprehensive about extended genomic technologies with concerns regarding disclosure results and 'designer babies'. Recipients felt the donor genetic information provided to them was sufficient and important. Recipients also recognized potential benefits of extended genomic screening (e.g. promoting wellbeing of child) but also disadvantages (e.g., reduced donor numbers). Further support and education in this area may assist donors and recipients to have a clearer understanding of genetic risks associated with gamete and embryo donation if extended genetic screening is implemented.

34. THREE GENES, GOOD VISION AND A BABY

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Background: For most inherited eye diseases, there can be very limited treatment options and for some people blindness is feared above death itself. Any inherited eye disease can have a high impact on reproductive decision making not only for affected individuals, but also parents of affected children and at risk family members. While advances in genetic testing have provided choices for family planning, in some cases the gift of genetic knowledge can have significant implications socially, ethically and financially for the whole family. *Aim:* To explore the reproductive challenges faced by families with inherited eye diseases. *Method:* Case presentation of three families each with an inherited eye disease and genetic change identified. *Discussion/Conclusion:* These cases emphasize that individuals at risk of having a child with an inherited eye condition require support, genetic counseling and maybe potential funding assistance to access Pre-implantation Genetic Diagnosis (PGD).

35. DECISIONAL NEEDS OF FAMILY MEMBERS OF INDEX BRCA CARRIERS FROM THE MALAYSIAN BREAST CANCER (MYBRCA) STUDY WHEN CONSIDERING PREDICTIVE GENETIC TESTING

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Background: Hereditary breast or ovarian cancer may have consequences beyond the index patient. Genetic testing therefore plays an important role in ascertainment of individual's risk so that decision making regarding appropriate risk management strategies can be facilitated. In Malaysia, although the communication of BRCA related information among families is high, uptake of testing was 11%. This is the first study conducted in Malaysia exploring family members experience in receiving or communicating BRCA related information within the family, and decisional needs for predictive BRCA genetic testing. *Methods:* A sample size of 20 was planned using maximal variation sampling. All first/second degree relatives of index BRCA 1/2 carriers from the MyBrCa study, who have attended predictive pre-test genetic counseling, unaffected with cancer and aged 21–69 years were invited to participate in this study. Relatives participated in a semi-structured qualitative in-person or telephone interview regarding family communication and their decisional needs for BRCA testing. Data will be analyzed thematically.

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Results: To date, 10 participants (7 Malays, 3 Chinese) have been interviewed. Preliminary results suggest that the preferred strategies to support communication of BRCA related information among families are an information seminar ($n = 5$) or support group ($n = 2$), leaflet ($n = 1$), communication prompt sheets ($n = 1$) or videos ($n = 1$). *Discussion:* Results from this study will be used to develop a culturally compatible intervention tool for family members considering predictive BRCA genetic testing. Through these initiatives, it is hoped that more at-risk family members in Malaysia will benefit from genetic counseling, testing and risk management strategies.

36. DEVELOPMENT OF A COMMUNICATION AID FOR EXPLAINING HYPERTROPHIC CARDIOMYOPATHY GENETIC TEST RESULTS

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Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder characterized by left ventricular hypertrophy. Large gene panels (>50 genes) are commonplace for HCM genetic testing, but interpretation is increasingly complex given the probabilistic nature of the result. Genetic counselors enable informed consent by ensuring that the patient understands the potential outcomes, clinical and familial implications, and limitations of genetic testing. Development of strategies to more effectively communicate this complex information is needed. We aim to pilot a genetic counselor-led intervention with a communication aid to facilitate the genetic result discussion in a specialized HCM centre. Based on clinical expertise and visual representation frameworks, the aid addresses (a) what genetic testing is, (b) what the result will tell a patient, (c) criteria that determines the classification of an identified variant and what it means, and (d) how the result impacts the patient's family. The aid is a booklet that is also suitable for take-home use. It is hypothesized that the intervention group will demonstrate higher levels of understanding, knowledge and satisfaction surrounding HCM genetics due to the use of the aid. A pilot randomized controlled trial of 30 HCM probands will be conducted, and a follow-up survey, containing validated scales and open-ended questions will be sent post-appointment to assess the effectiveness and feasibility of the intervention. HCM probands due to receive their genetic test result between May-July 2016 will be eligible. We hope this will be a basis to further improve our communication of complex information to families with genetic heart disease.

37. EVALUATION OF THE GENETIC INFORMATION SYSTEM (GIS) AS A SHARED DATABASE ACROSS NEW SOUTH WALES (NSW) AND AUSTRALIAN CAPITAL TERRITORY (ACT) GENETICS SERVICES

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The Genetic Information System (GIS) is an electronic genetic health management system that was implemented in NSW and the ACT in August 2010 and May 2013 respectively. It is a state-wide system that stores information in family files within genetics services. Benefits of the system have been anticipated with respect to clients, genetic health professionals and NSW and ACT Health Departments, however, no formal research has been performed. Benefits for other health information technology (IT) systems such as patient management systems and health registries have been described and are similar to those anticipated for the GIS. This research aims to explore the benefits and challenges of the GIS as a shared database across NSW and ACT genetics services, to provide insight into how the database has impacted on patient administration and service delivery. A qualitative study with genetic counselors ($N = 15$) employed in NSW or ACT genetics services with professional experience before and after the introduction of the GIS will be conducted. Recruitment will be through ethically approved email invitations for thirty minute phone interviews. The qualitative data will be analyzed and coded by three researchers and themes will be identified. The study results will provide insight into how a shared database has impacted on patient administration and service delivery within genetic services. It may also inform future proposals for genetic service databases that are shared across state boundaries.

38. COMMUNICATION OF CARDIAC GENETIC RISK INFORMATION AMONG FAMILIES IN SINGAPORE

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The genetic nature of inherited cardiac conditions (ICCs) places first- and second- degree relatives at risk of cardiac complications and sudden death, even in the absence of symptoms. Family communication allows at-risk relatives to clarify, manage, and prevent ICC-associated risks through cardiac screening, and sometimes even genetic testing. Current literature on family communication of genetic risk information are predominantly based on Western populations, with no available Singaporean literature. This qualitative exploratory research study explored communication of ICC risks within families in Singapore to guide current cardiac genetic counseling practices, and inform the development of other genetic counseling services. Eight male participants were recruited from a prior ethics-approved study at the National University Heart Centre, Singapore. Seven were clinically diagnosed with HCM and one with DCM, and all had received genetic counseling. Semi-structured interviews were conducted, audio-recorded, and transcribed verbatim. Anonymized interviews were independently analyzed and coded. Emerging themes were grouped and collectively refined through an iterative process. Participants understood the ICC risk and all communicated risk information to more than one first-degree relative. Motivators of family communication include pre-existing patterns of open communication and healthcare professionals' encouragement to inform, while physical and emotional inadequacies contributed to passive non-disclosure. Understanding these barriers allows the development of strategies to overcome them. Notably, at-risk relatives were described as presently asymptomatic and healthy, and not accessing screening. Fear of detecting cardiac issues through screening was a postulated deterrent. Findings highlight key areas for genetic counseling support, especially the need to overcome barriers against screening.

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39. UNDERSTANDING THE EXPERIENCES AND NEEDS OF PEOPLE WITH HEREDITARY HAEMORRHAGIC TELANGIECTASIA

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a hereditary condition which causes severe nosebleeds in upwards of 90% of affected individuals, as well as life-threatening complications in organs such as the lungs, spine, and brain. Only limited international psychosocial research on the condition exists, and no psychosocial research has been undertaken in Australian populations. *Aim:* To understand the impact of HHT on the daily life of affected individuals in Australia and what, if any, supports could be of benefit to these individuals. *Method:* Semi-structured interviews were conducted with eight individuals with HHT about their experiences with HHT using a phenomenological framework. Interviews were then transcribed and coded using thematic analysis to elicit common themes. *Results:* Participants spoke about their experiences of interacting with healthcare professionals who they frequently felt did not have an adequate knowledge of HHT. However, participants described that this often led to them to be more proactive about self-managing their own health. Anxiety was raised as an example of the personal impact of HHT. Participants spoke about the impact symptoms of HHT had in social and work settings, though many people preferred to avoid focusing too much on HHT in their life. *Conclusion:* Participants felt that better understanding and coordinated care from healthcare professionals is needed. A strong theme of the desire for a Centre of Excellence in Australia was identified, as was a theme of the importance of peer support, particularly around times of high anxiety such as testing and receiving results.

PRENATAL DIAGNOSIS

40. SPLIT HAND/FOOT MALFORMATION, CLEFT LIP/PALATE, AND SEVERE UROGENITAL ABNORMALITIES — SIBLING RECURRENCE DUE TO GERMLINE MOSAICISM FOR TP63 MUTATION

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An unrelated couple were referred after two consecutive pregnancies complicated by detection of severe urogenital abnormalities on prenatal ultrasound. Post-delivery examination after termination of pregnancy showed that both fetuses had bilateral split hand and foot malformation (SHFM) and bilateral cleft lip and palate. These findings are consistent with the ectrodactyly, ectodermal dysplasia, cleft lip with or without cleft palate syndrome (EEC). Both fetuses were found to have the same missense mutation in TP63 (c.1051G>A; p.D351N). Parental clinical examinations were normal and neither parent had evidence of the mutation on Sanger sequencing of lymphocyte DNA. Although urogenital anomalies have been reported in some individuals with TP63-related disorders, the malformations here were unusually severe, and so far genotype:phenotype correlations are limited. This recurrence in siblings also highlights the need to counsel for the possibility of germline mosaicism in TP63-associated disorders.

41. OUTCOME ANALYSIS OF 28 NIPT CASES WITH INCREASED RISK FOR TRISOMY 13

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Background: Non-invasive prenatal testing (NIPT) is a highly accurate screening test for the detection of fetal chromosomal aneuploidies involving trisomies 13, 18 and 21. However, confirmation rates after diagnostic testing are lower for Trisomy 13 (T13) when compared with the other trisomies. *Aim:* We present our experience with 28 cases of increased risk results for T13 identified in patients undergoing percept^{TM} NIPT and assess the potential contribution of confined placental mosaicism (CPM) in explaining false positive test results. *Methods:* We reviewed 28 patients with High or Intermediate Risk results for T13 identified from approximately 10,000 NIPT referrals. Cases were followed with diagnostic testing using direct interphase FISH analysis, Long term mesenchyme CVS culture and/or amniotic fluid karyotype/microarray analysis. Examination of placental biopsies after delivery was also attempted in some cases of suspected CPM. *Results:* Of 24 High Risk results, 15/24 (63%) cases were confirmed as T13. Placental biopsy material was available in 4 of 9 cases with normal karyotype. CPM for T13 was identified in 3 of 4 cases (75%), indicating that CPM is a common cause of false positive findings. For Intermediate Risk results (4 cases), 3 showed normal karyotype after diagnostic testing while one case is awaiting follow up but has normal ultrasound. Placental biopsy in one of these cases failed to identify T13 cells. *Conclusion:* CPM is a common cause of false-positive NIPT results for T13. Patients with High Risk T13 results with normal ultrasound might consider amniocentesis instead of CVS for confirmatory diagnostic testing.

42. FAMILIAL RETINOBLASTOMA AND GENETIC TESTING: A PARADIGM SHIFT IN CLINICAL CARE

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Background: Retinoblastoma (RB) is the most common intraocular malignancy occurring in children. The RB1 gene was first identified in 1986 with genetic testing for RB translating to clinical care by the end of the 1990's. This heralded a paradigm shift in the clinical management of affected individuals by informing their clinical care and that of their siblings and offspring. *Aim:* To report on the frequency and outcomes of the use of pre- and post-natal genetic testing for familial retinoblastoma using the Victorian Retinoblastoma Database cohort since 1998. *Methods:* Retrospective audit of the Victorian Retinoblastoma Database. *Results:* Twenty-six infants were born of 13 individuals with a personal or family history of RB. Only 4 of the 13 parents elected to undergo pre-natal testing for 7 pregnancies. Pre- or postnatal genetic testing was completed in 19 pregnancies. Of these, 12 (63%) infants were found to carry their familial RB1 mutation, 6 of whom remain unaffected carriers. Five of the unaffected carriers are from 2 known low-penetrant families.

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The gestational age at which the first lesions developed in all the affected infants ranged from 35 to 43 weeks (mean 40 weeks). One pregnancy was induced due to the identification of lesions prenatally with intrauterine MRI. With treatment, 21 eyes of 12 affected children have been retained.
Conclusion: Timely genetic counseling and testing for individuals with a personal or family history of RB is an integral part of optimal clinical care. This multi-disciplinary approach to care and surveillance is vital to ensure the earliest diagnosis and treatment for optimal outcomes.

43. PICKING UP THE PIECES: AN EXPLORATION OF PATIENTS' AND PRACTITIONERS' EXPERIENCES OF DETECTION OF A FETAL ANOMALY AT ULTRASOUND TO INFORM GENETIC COUNSELING PRACTICE

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Background: When a fetal anomaly is detected during ultrasound, ultrasound practitioners' verbal and non-verbal communication, and disclosure of information may influence pregnant women's experiences, including their process of decision-making. Little is known about how practitioners make decisions regarding disclosure, what formal or informal training they receive, or practice protocols surrounding immediate care of women and couples. *Aim:* To explore experiences of detection of fetal anomaly from two perspectives: women/couples; and prenatal ultrasound practitioners. Additionally, practitioner training and practice protocols will also be investigated in order to triangulate the data. *Method:* (1) Thematic analysis of data from an existing study exploring experiences of women and men who received a prenatal diagnosis (the PeTALS project (prenatal testing: a longitudinal study), focusing on experiences of detection of fetal anomaly at ultrasound; (2) Inductive content analysis on semi-structured interviews with prenatal ultrasound practitioners, focusing on personal experiences and training regarding disclosure and practice protocols.
Results: Patients' ($n = 102$) experiences identified that practitioners' non-verbal behaviors, language use, perceived non-empathic manner and lack of immediate information contributed to distress and angst. Recruitment of prenatal ultrasound practitioners (anticipated $n = 20$) is ongoing and will further explore the challenges of supporting patients at this time. *Discussion/Conclusions:* Patient experiences highlight aspects of ultrasound practice that contribute to distress which the woman/couple may bring to their encounters with genetic counselors. A greater understanding of the variability patients experience at ultrasound can assist genetic counselors to better support women and couples who receive a prenatal diagnosis of fetal anomaly detected by ultrasound.

44. WITHDRAWN

45. A FAMILY HISTORY OF ATYPICAL DMD AND GENETIC COUNSELING FOR AN UNUSUAL MOLECULAR FINDING LATE IN PREGNANCY

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Genetic counseling in the prenatal setting is continually challenging. We present the case of SR and her partner who were referred at 16 weeks in pregnancy for prenatal counseling regarding a family history of atypical DMD. SR was in her first pregnancy and has a brother affected with atypical DMD. Her brother TR, is 25 years of age, is severely disabled by his illness with worsening respiratory function. He was diagnosed in a clinical genetics service at 9 years of age. Molecular testing performed in 1999 failed to detect a deletion in the DMD gene. There was no other family history of DMD. Ultrasound examination at 16 weeks confirmed a male pregnancy in SR. She was certain that she wanted to avoid having a son with DMD. Urgent MLPA testing was initiated on the brother and this returned a negative result. DMD gene sequencing followed and a rare variation of unknown significance (VUS) with high clinical significance was identified in the brother. This variant is not present in databases of normal human variation and has been described in one other case of DMD in China. Carrier testing identified that SR carried the same variant. SR proceeded with a CVS at 20 weeks and the variant was found in the male fetus at 21 weeks. The difficulties for SR and her family will be discussed and the counseling issues will be explored, highlighting the complexities for both the patient and counselor in a limited timeframe.

46. HB BART'S HYDROPS FETALIS (BHF): IS IT BEING MISSED IN THE AUSTRALIAN PREGNANT POPULATION?

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Normal individuals have four hemoglobin alpha genes, two in tandem on each allele (HBA2 and HBA1). Carriers of alpha thalassemia can have one gene deleted (silent carriers of alpha thalassemia), two genes deleted in cis (alpha zero thalassemia), three genes deleted (HbH disease) or all four genes deleted resulting in alpha thalassemia major which is incompatible with life. If both parents carry alpha zero thalassemia, the fetus has a ¼ risk of alpha thalassemia major, having no functional hemoglobin alpha genes. This leads to the formation of high oxygen affinity hemoglobin which prevents normal oxygen transport, called Bart's hemoglobin. The fetus develops multiple congenital abnormalities, including cardiac failure resulting in Bart's hydrops fetalis (BHF). Death occurs in utero or shortly after birth. As the incidence of BHF is poorly documented in Australia, we report our 25-year experience with the diagnosis of this disorder. Between 1990–2015, 97/410 (24%) PND were performed for alpha thalassemia, with 26/97 (27%) affected pregnancies. We present two cases: (1) a stillbirth with BHF and (2) a woman with four stillbirths and hydrops detected in her fifth pregnancy after red cell indices alerted laboratory staff to heterozygosity for alpha zero thalassemia. Partner testing revealed alpha zero heterozygosity in the father. PND and genetic testing after termination of pregnancy confirmed a diagnosis of BHF. Our data highlights the value of screening pregnant women with microcytic hypochromic blood pictures for alpha thalassemia to facilitate early detection of couples at risk of BHF.

47. WITHDRAWN

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48. NON-INVASIVE PRENATAL TESTING FOR SEX CHROMOSOME ANEUPLOIDY IN ROUTINE CLINICAL PRACTICE.

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Background: There is limited data on the use of NIPT for screening of common aneuplodies in routine clinical practice, particularly in relation to sex chromosome aneuploidies (SCA). *Aim:* To assess the accuracy of NIPT for SCA with consideration of counseling and sonographic issues. *Methods:* Three private practices specializing in obstetric ultrasound and prenatal diagnosis in Australia offered NIPT for singleton pregnancies after 10 weeks gestation. Findings for validated chromosomes 21, 18, 13, X and Y were reported. *Results:* NIPT was performed in 5267 women and was a first-line screening method in 3359 (63.8%). Overall, 120 high-risk results were reported, with 60 (50%) being SCA. Invasive testing via CVS or amniocentesis was elected by 40 (67%) patients with high-risk SCA results, in comparison to 51 (85%) following a high-risk autosomal aneuploidy result. Thirty-three (55%) high-risk SCA results were found to be false positives giving an overall positive predictive value (PPV) of 36.5%, with the lowest PPV being for Monosomy X at 28%. *Conclusions:* Inclusion of sex chromosomes in NIPT is often desired by couples for early indication of fetal sex, however our results bring into question their routine inclusion. False positive screening results are recognised to increase maternal anxiety in the long-term and have been shown to reduce uptake of prenatal screening in subsequent pregnancies. More comprehensive counseling for the inclusion of sex chromosomes may be required to balance the risk of false positive results with the opportunity to antenatally diagnose some forms of intersex and ambiguous genitalia.

NEUROGENETICS

49. THE EFFICACY OF THE TARGETED NEXT GENERATION SEQUENCING PANEL IN DIAGNOSIS OF MONOGENIC NEUROLOGICAL DISORDERS

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Episodic ataxia type 2 (EA2) is a rare autosomal dominantly inherited neurological disorder characterized by recurrent disabling imbalance, vertigo and episodes of ataxia lasting minutes to hours. Frequency of attacks ranges from once a year to four times a week. EA2 is caused most often by loss of function mutations of the calcium channel gene (CACNA1A), which encodes the CaV 2.1 subunit of the P/Q-type calcium channel and is widely expressed in Purkinje cells. Mutations in the CACNA1A gene were found to be responsible for two allelic disorders with autosomal dominant inheritance in addition to EA2: familial hemiplegic migraine type1 (FHM1) and spinocerebellar ataxia type 6 (SCA6). Overlapping clinical features of these allelic disorders have been previously described. It is thus often difficult for clinicians to diagnose the specific disorders present in a patient. In this study, we have utilized Next Generation Sequencing (NGS) to screen the coding sequence, exon-intron boundaries and Untranslated Regions (UTRs) of five genes. We performed this mutational screening in a group of 31 unrelated patients with EA2. Both novel and known mutations were detected, with all identified novel mutations confirmed through Sanger sequencing. The genetic analysis identified 15 patients with mutations (48%), of which 9 were novel (6 missense and 3 frameshift deletion mutations) and six known mutations (4 missense and 2 nonsense). The results of this study indicate that targeted NGS technology is capable of identifying known and novel mutations to aid in the diagnosis of familial neurogenetic disorders.

50. RECESSIVE PORPHYRIA DUE TO HOMOZYGOUS HMBS MUTATION: A CAUSE OF LEUKODYSTROPHY WITH CATARACTS

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We have identified a new genetic and potentially-treatable cause for leukodystrophy with cataracts and expanded the known phenotype associated with the rare occurrence of recessive acute intermittent porphyria (AIP). Two adult siblings from a consanguineous family were referred for whole exome sequencing (WES) as part of a gene discovery project investigating unclassified leukodystrophies. They share a novel phenotype characterized by leukodystrophy, childhood-onset cataracts, progressive ataxia, lower limb spasticity and peripheral neuropathy. Their cerebral MRI shows periventricular demyelination with thalamic cavitations. WES identified a homozygous variant in HMBS (c.251C>A, p.A84D) in both affected siblings. Their parents and two unaffected siblings were found to be heterozygous for this variant. The pathogenicity of this variant has been demonstrated by reduced erythrocyte HMBS activity in the proband to 20% normal. Heterozygous variants in this gene cause acute intermittent porphyria (AIP), a dominantly inherited neurological disorder with reduced penetrance. Only six cases of recessive AIP have been reported, all presenting in early childhood with severe central and peripheral neurological impairment, four with childhood onset cataracts and one found to have leukodystrophy. All had <4% of normal HMBS activity and died in childhood. The level of residual HMBS activity appears to correspond with disease severity. There are no reported cases of adults with recessive AIP and so this finding represents a novel phenotype and a new genetic cause for leukodystrophy with cataracts. The less affected of the two sibs is being worked up for liver transplantation with the aim of halting progression of this neurodegenerative disorder.

51. UTILIZING THE BENEFITS OF WHOLE EXOME SEQUENCING TO ADVANCE EFFORTS IN FAMILIAL HEMIPLEGIC MIGRAINE DIAGNOSTICS

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Familial hemiplegic migraine (FHM) is a restrictive and intense neurological condition. Attacks are often characterized by severe head pain, nausea, aura, phono/photophobia and in extreme instances hemiparesis. Due to limitations in analytical technologies, current diagnostic success rates are low, treatment is sub-par and the understanding behind the pathophysiological consequence of gene-phenotype association is constrained. We will apply the in-depth

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sequencing capabilities of whole exome sequencing (WES) technology to examine a cohort of clinically suspected and genetically undiagnosed FHM patients for potential new diagnostic markers. Using a bioinformatics modeling approach, we have developed analysis of the sequencing data filtering variants based on gene ontology and minor allele frequencies, along with a number of functional scores. Preliminary results have revealed some interesting candidate genes supporting the use of WES for the identification of new FHM implicated genes. This research should aid in obtaining a more complete understanding of the genetic basis of FHM, advance efforts in FHM diagnostics and effectively improve overall patient outcomes.

52. NEUROGENETIC DIAGNOSTICS FOR SEVERE MIGRAINE, EPISODIC ATAXIA, CADASIL AND EPILEPSY

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Migraine is a common neurological disorder affecting ~12% of the Caucasian population. Several rare inherited neurological disorders are associated with migraine. Epilepsy is closely linked to migraine with a prevalence of 6% in migraineurs compared to 0.5% in non-migraineurs. Both migraine and epilepsy share a number of common symptoms including: post-event lethargy, impaired or loss of consciousness, visual and hormonal triggering factors, anesthesias, vertigo, visual disturbances, aphasia and hemiparesis and aura symptoms. At least one of the three genes that cause the rare subtype of migraine, familial hemiplegic migraine (FHM), can also cause epilepsy. However, the genetic basis for these complex migraine subtypes and their co-morbidity with epilepsy remain unclear. Recently, we have utilized Next Generation Sequencing (NGS) to develop a more effective diagnostic test for FHM, epilepsy and related disorders. We designed an NGS AmpliSeq custom panel to use on an Ion Torrent/Proton platform that screens the coding regions, exon-intron junctions, 5'-UTR and 3'-UTR regions of all three FHM genes (CACNA1A, ATP1A2 and SCN1A), as well as the NOTCH3 and TRESK genes implicated in the stroke syndrome CADASIL and familial migraine. The NGS targeted neurogenetic panel represents a significant improvement in molecular genetic testing in terms of cost and speed of diagnosis and also allows more targeted treatment choices. We have also recently developed a whole exome approach with an analysis pipeline to enable diagnosis of these disorders, as well as to aid in identifying novel genes.

53. THE GENETICS OF DEVELOPMENTAL PROSOPAGNOSIA (FACE-BLINDNESS) – A PILOT STUDY

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Developmental prosopagnosia is the inability to recognize faces, the disability evident from childhood, in persons typically otherwise of normal neurological health. The condition can be embarrassing and a social encumbrance. The defect is believed to lie in dedicated neurones within the fusiform face area of the right occipito-temporal gyrus. Numerous reports of familial cases are on record, and in some families the picture is suggestive of an autosomal dominant gene. We studied 10 persons with presumed developmental prosopagnosia, some apparently sporadic cases, and some with similarly affected relatives. DNAs prepared from saliva samples were subjected to a whole exome study at otogenetics, and these data analyzed in-house. In the event, no candidate variants common to at least some of the participants were identified. The genetics of developmental prosopagnosia remains to be elucidated. It seems likely that collaborations to achieve greater numbers may be needed.

54. BRAT1-ASSOCIATED NEURODEGENERATION: INTRA-FAMILIAL PHENOTYPIC DIFFERENCES BETWEEN A SEX-DISCORDANT SIBLING PAIR.

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We identified a family consisting of a sex-discordant sibling pair with progressive microcephaly, multifocal seizures and premature death at 15 months of age in the male sibling. Since the parents were unaffected and not known to be related, autosomal recessive inheritance was predicted. To identify the genetic cause in the family, whole exome sequencing in three family members was performed. Compound heterozygous truncating mutations were identified in BRAT1, coding for BRCA1-associated ATM activator 1, which plays a role in double stranded DNA repair, in both siblings. Recessive mutations in BRAT1 cause lethal neonatal rigidity and multifocal seizure syndrome (OMIM #614498), a phenotype characterized by neonatal microcephaly, hypertonia and refractory epilepsy with premature death by 2 years of age. The attenuated phenotypes described here and elsewhere suggest a wider clinical spectrum of BRAT1-associated neurodegeneration exists. Mutation-specific effects are likely to play a role in this phenotypic variability: Truncating mutations in the family described here are located in the last exon of the gene and are not predicted to cause nonsense-mediated decay of the mutant transcripts, unlike mutations described in more severe cases. However, this does not account for the sibling discordance reported, suggesting that sex-specific modifying factors might reduce BRAT1-related disease severity in females, as observed in related DNA repair mechanisms.

Further interrogation of this phenotypic variability is warranted and may impact therapeutic approaches to patient management. Moreover, the existence of mildly affected individuals necessitates consideration of BRAT1-associated disease in cases of childhood refractory epilepsy and microcephaly with survival beyond infancy.

55. ALTERED EXPRESSION OF LONG NONCODING RNA NEAT1 IN HUNTINGTON'S DISEASE

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Huntington's disease (HD) is a devastating neurodegenerative disease caused by cytosine-adenine-guaninetrinucleotide repeat expansion in the huntingtin gene. Growing evidence supports the regulatory functions of long noncoding RNAs (lncRNAs) in the disease processes, we still know little about the association between lncRNAs and neuronal death in HD. Here, we evaluated the altered expression profiles of lncRNA in HD by using microarray. Among dysregulated lncRNAs, we focused on the upregulation of nuclear paraspeckle assembly transcript 1 (NEAT1). QuantitativePCR analysis validated increased NEAT1 levels in the R6/2 mouse brain as well as the human HD postmortem brain. To determine the biological effects of NEAT1 on neuronal survival, neuro2A cells were

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transfected with NEAT1 vector and subjected to H2O2-induced injury. As a result, NEAT1-transfected cells showed increased viability under oxidativestress. Our observations support the notion that NEAT1 upregulation in HD contributes to the neuroprotective mechanism against neuronal injury rather than the pathological process underlying neurodegeneration in HD.

56. CEREBRAL AUTOSOMAL RECESSIVE ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CARASIL): THE FIRST AUSTRALIAN CASES

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Objective: Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL) is a rare autosomal-recessive cerebral small vessel vasculopathy caused by mutations in the HTRA1 gene. This gene encodes HtrA serine peptidase/protease 1 which represses signaling by transforming growth factor-β family members. Most of the 50 cases described are ethically Asian (from Japan and China) and there are very few reports of Caucasian patients. *Method:* Description of the clinical presentation, imaging characteristics and genetic studies of two siblings with CARASIL and phenotypic and genetic comparison with cases from the literature. *Result:* Both patients presented with step-wise neurological symptoms and typical leukodystrophic MRI changes but lacked the usual additional features of acute back pain and abnormal hair loss. Testing for NOTCH3 was negative but both patients carried biallelic pathogenic mutations in the HTRA1 gene. The first mutation is documented as c.184_185del, the second variant as c.821g>A. *Conclusion:* These sisters are the first Australian cases of CARASIL described and add to the population of non-Asian cases in the literature. The phenotype is interesting due to the absence of alopecia and back pain. We suggest that HTRA1 testing should be considered in cases where clinical history and imaging is suggestive of a small vessel arteriopathy with leukodystrophy but NOTCH3 testing is negative.

57. A CASE 'OUT OF THE BLUE'

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Objective: To delineate a retrospective diagnosis in a case of severe fixed encephalopathy. *Case Description:* Propositus was a male child, born to consanguineous South Asian parents. During the first months of life, he had generalized hypotonia with dystonic leg extension spasm and frequent vomiting. Child never attained any developmental milestones. From his photographs head size appeared to be small and esotropia and adducted thumbs were noted. He had gradeII/III GERD. His MRI brain showed delayed myelination. All other investigations including neurometabolic and electrophysiological analysis were within normal limits. He was treated as cerebral palsy without much improvement to the symptoms. Child expired at the age of 2 years after an attack of pneumonia; clinical exome was performed later from his DNA. *Results:* Long read sequencing revealed a novel, homozygous, pathogenic exonic deletion in CYB5R3 gene, associated with recessive hereditary methemoglobinemia (RHM) type II, which could explain the clinical profile. This large deletion was validated by PCR and carrier status of parents was established. *Conclusion:* Type II RHM is a rare condition, with less than 100 cases reported worldwide. Cyanosis is an invariable presenting feature and important clinical clue to methemoglobinemia. There was no history or documentation of cyanosis in our case. In the absence/failure to elicit the sign in children with severe encephalopathy, possibility of RHM might get overlooked. Reported mutations in RHM type II, so far, are point mutations. Ours is the first family with a large exonic deletion of CYB5R3 gene, thus expanding the genotype spectrum.

CLINICAL GENETICS

58. UNRAVELLING THE METABOLIC AND NEUROVASCULAR SPECTRUM OF THE 17q12 DELETION SYNDROME

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Summary: The 17q12 deletion syndrome is a common cause of neurodevelopmental delay with a proportion of patients developing renal cysts and diabetes (RCAD; MIM 137920) due to the deletion of HNF1β, a transcription factor with protean effects particularly in renal and pancreatic development. Additional features include mild dysmorphism, hyperuricemia, hypomagnesemia and dyslipidemia due to insulin resistance. The phenotype varies, and the deleted minimum critical region ranges from 1.06 to 1.52 Mb. Cognitive impairment, previously not known to be associated with this deletion syndrome, has recently been described. We present a case of 17q12 deletion syndrome in which the proband's manifestations (cognitive impairment, recurrent multi-territorial strokes and diabetes) were unmasked and worsened with pregnancy. The diabetes seen in this patient did not suggest decreased insulin secretion contrary to that typically seen in 17q12 deletion/ HNF1β-related disease and lipid profile was not suggestive of insulin resistance. We address the endocrinological, genetic and neurovascular issues in our patient, propose a mechanism for pregnancy providing a 'second hit' causing our patient's symptoms, and a potential metabolic pathway of the role of hypomagnesemia in urate balance in our patient. *Take home message:* 17q12 deletion syndrome is a multifaceted disorder, and its metabolic and neurologic manifestations may present later in life following physiological stress (e.g., pregnancy).

59. WITHDRAWN

60. APRT DEFICIENCY AND THE COMPLEXITIES SURROUNDING RENAL TRANSPLANTATION

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Adenine phosphoribosyl transferase (APRT) is an enzyme involved in the purine metabolism pathway. It metabolises adenine into the more soluble by-product adenosine monophosphate. Deficiency of APRT causes accumulation of 2,8-dihydroxyadenine, which is poorly soluble in urine and can lead to nephrolithiasis as well as chronic kidney disease (CKD) from crystal nephropathy. APRT

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deficiency is a rare autosomal recessive disorder. We present a family with APRT deficiency where the consultand has developed end stage renal failure due to crystal nephropathy. His current treatment options, including the chance of recurrence if renal transplantation is considered, are discussed below. The ethical issues surrounding kidney donation by a member of this family are also discussed.

61. TRIAGING COMPLEX CASES FOR GENETIC TESTING IN SOUTH AUSTRALIA: A MULTI-DISCIPLINARY TEAM APPROACH

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New genetic testing platforms offer much promise, but remain a limited resource in diagnostic settings. To maximize clinical utility, our diagnostic service has implemented a structured triage process. Tests are determined to be either 'standard testing' or 'case requiring review' (complex or panel precedent cases). The review process uses a multi-disciplinary team (MDT) forum, with structured case presentations and decision criteria to assist determination of the most appropriate testing. The review process includes consideration of management implications, evidence supporting genetic testing indication and utility, test availability, service capacity and in-house expertise, as well as expected turnaround time. A recommendation for each case is formed after open and robust discussion between the MDT meeting members (primary clinicians, pathologists, medical scientists and bioinformaticians). In 18 months, next-generation sequencing has replaced classical genetic testing as the platform of choice for more than 800 standard tests (especially for large genes). In addition, the consensus-based, open discussion MDT platform has reviewed 80 complex clinical cases over this period. The majority of complex cases have been pediatric patients, with the greatest number referred from clinical geneticists; however, immunologists, neurologists, cardiologists, metabolic, renal and general physicians have also been represented. A summary of the MDT system, with range of outcomes, phenotypes and results encountered will be presented. This approach reflects a paradigm shift in clinical review meetings, where embedding medical scientists with pathologists and primary physicians in an active clinical conversation maximises the utility of diagnostic services and assists best clinical outcome for patients.

62. EARLY ADOPTION OF GENETIC TESTING TECHNOLOGIES IN THE NICU — IMPACT ON DIAGNOSIS

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Background: Rare genetic diseases are a leading cause of morbidity and mortality in neonatal intensive care units (NICUs). Accurate and timely genetic diagnosis in this patient group can prevent unnecessary investigations, rationalise treatment, and provide prognostic and recurrence risk information to families. *Aim:* To examine the impact of the early adoption of genetic testing technologies, in particular chromosomal microarray (CMA) and whole exome sequencing (WES) on the rate of diagnosis in infants referred for genetics consultation by NICU. *Methods:* Retrospective review of medical records of infants referred by NICU for genetics inpatient consultation in 2007 (pre-CMA), 2011 (post-CMA) and 2015 (post-WES) at the Royal Children's Hospital, Melbourne. Data were collected on referral indications, and the rate of clinical and molecular diagnosis achieved within the first year of life. *Results:* Of 44 neonatal inpatients referred for genetics opinion in 2007, 34 (77%) were thought to have an underlying genetic condition with a diagnosis confirmed in 7 (20%) through genetic testing, primarily standard karyotype. Referrals in 2015 more than doubled, with 104 patients assessed. Sixty-four patients (61.5%) were thought to have an underlying genetic condition, with 32 (50%) receiving a confirmed molecular diagnosis to date, the majority being monogenic disorders. *Conclusion:* The early adoption of new genetic testing technologies in NICU patients referred for genetics consultation at our centre has resulted in a significant increase in the rate of confirmed genetic diagnoses over a period of 8 years, with a shift in diagnosis types from primarily chromosomal abnormalities to monogenic disorders.

63. THE PHENOTYPIC AND GENOTYPIC SPECTRUM OF MAYER-ROKITANSKY-KUSTER-HAUSER SYNDROME

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Background: Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) affects 1/4500 females and is characterized by agenesis of Mullerian structures including the uterus, cervix and upper vagina. It can occur in isolation (Type 1) or in conjunction with associated anomalies (Type 2). The genetic causes of MRKH have been investigated previously yielding limited results, however massive parallel sequencing has rarely been utilized. *Objectives:* We sought to clinically characterize the phenotypic spectrum of anomalies associated with MRKH. We also aimed to identify the genetic causes of Types 1 and 2 MRKH, using chromosome microarray, targeted MLPA, and massive parallel sequencing. *Methods:* We searched medical records of The Royal Children's Hospital, Victorian Clinical Genetics Services and Murdoch Children's Research Institute for patients with MRKH. Potential participants were contacted by clinicians to obtain informed consent. We initially undertook SNP microarray, and in those in whom no diagnostic copy number variants were identified, we used a targeted MLPA and a DSD (disorder of sex development) gene panel. Whole exome sequencing was undertaken in those with no diagnostic results from prior tests. *Results:* We identified 20 females with Type 1 ($n = 2$) and Type 2 ($n = 18$) MRKH aged between 15–27. The spectrum of anomalies observed included those affecting renal, craniofacial, skeletal, gastrointestinal, cardiopulmonary and neurological structures. Results of MLPA, gene panel and whole exome sequencing will be presented. *Conclusions:* MRKH is a rare malformation syndrome that is clinically and causally heterogeneous. Further functional studies are required to delineate the biological significance of the variants identified by massive parallel sequencing.

64. DELETION AT CHROMOSOME 10p12.1 CONTAINING WAC GENE, IS IT A NEW DELETION SYNDROME

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Background: More and more new deletion syndromes are being discovered. Information in the literature suggests that deletion at chromosome 10 including WAC gene is a new deletion syndrome. Methods: A written consent was taken from the family to show patient's photographs in any academic meeting and a potential pub-

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lication. History: (1) global developmental delay, (2) intellectual disability, (3) past history of epilepsy, (4) precocious puberty (5) sleep problems, (6) Perthes disease, (7) knee joint dislocation needing orthopedic intervention, (8) bilateral genu valgum deformity, (8) planovalgus deformity. *Examination:* (1) short stature, full cheeks, bulbous nose, synophrys; (2) short neck, small hands and feet; (3) hirsutism. *Results:* Microarray showed a de-novo deletion of size 1.2 Mb at chromosome 10p12.1(coordinates 27554385–28830108). This area of chromosome contains six OMIM genes including WAC gene. *Discussion:* The patients reported in the literature with similar deletions, all including WAC gene, had developmental delay, motor and speech delay, dysmorphic features like thick eye brows, deep set eyes and bulbous nose. Some patients with an overlapping phenotype have a deletion at chromosome 10p12-p11 encompassing several genes and consistent with a contiguous gene deletion syndrome. *Conclusion:* We believe that like many other deletion syndromes, deletion at chromosome 10p12.1 containing WAC gene is a new deletion syndrome. More and more information is useful to expand the phenotype.

65. CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH SHOX DUPLICATION

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Haploinsufficiency of the SHOX gene and deletions involving the 3' regulatory region are well documented to cause Idiopathic Short Stature (ISS) and variable skeletal abnormalities such as Léri-Weill Dyschondrosteosis (LWD) and Langer Mesomelic Dysplasia (LMD). In contrast, it has been postulated that having additional copies of the SHOX gene is associated with normal to tall stature. Recently, intragenic SHOX duplications and duplications of 3' long-range enhancers, which are the evolutionary conserved sequences/conserved non-coding DNA elements (ECSs, or CNEs), have been described to cause SHOX-related phenotypes. The aim of this review is to further evaluate the role of these duplications in SHOX-related disorders. We reviewed the records of patients who were seen in the Genetics clinic at KK Women's and Children's Hospital and had chromosomal microarray analysis (CMA) using the Agilent 4x180K CGH+SNP array at DNA Diagnostic & Research Laboratory. We provide detailed molecular cytogenetic descriptions and clinical presentations of three unrelated patients. At Xp22.33, Patient 1 has a 0.256Mb duplication (chrX:349,740-605,830 hg19), Patient 2 a 0.329Mb duplication (chrX:330,851-659,369 hg19), and Patient 3 a 0.345Mb duplication (chrX:286,328-631,854 hg19). The indications for CMA in these patients included a variety of phenotypic abnormalities. The SHOX duplication, not involving downstreams ECSs, was interpreted as a variant of uncertain significance, likely benign. The height percentiles for our patients are: 25–50th for Patient 1, 3–10th for Patient 2 and 25–50th for Patient 3. Our present data does not provide further evidence that duplications of SHOX gene and its long-range enhancers can result in a SHOX-related phenotype.

66. COMPOUND HETEROZYGOUS MUTATIONS IN FBN1 IN A LARGE FAMILY WITH MARFAN SYNDROME

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Background: Marfan syndrome (MFS) is caused by mutations in FBN1 but there is considerable inter and intra-familial phenotypic variability. This variation is usually attributed to genetic modifiers, epigenetic and/or environmental effects. We performed whole exome sequencing (WES) on a subset of affected individuals from a large kindred with MFS to identify potential genetic modifiers. *Method:* Clinical and genetic samples were collected from 43 members of the kindred. WES was carried out in 14 individuals meeting diagnostic criteria for MFS. *Results:* A previously identified FBN1 missense mutation (p.Tyr754Cys) was confirmed in all subjects. A second FBN1 mutation (p.Met2273Thr) was identified in a single affected individual. Sanger sequencing confirmed that the mutation originated from the reportedly unaffected mother though dilatation of the aorta was diagnosed at 68 years. Given her age and history of hypertension the significance is unclear. Two of the proband's siblings were also compound heterozygotes while another two carried only the original (Tyr754Cys) mutation. There is considerable phenotypic variability between the three compound heterozygotes though they did have cardiac complications at an earlier age than their siblings who carried the Tyr754Cys mutation alone. *Conclusion:* Compound heterozygosity or homozygosity is rare in MFS and in both previous reports the phenotype was more severe in family members with two variants. In this pedigree carrying both variants appears to be associated with the age of onset of aortic root dilatation but it does not explain all the clinical variability, indicating the presence of other modifiers.

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67. WHAT TO DO WITH MY PATIENT'S NOVEL VARIANT? COLLABORATE, COLLABORATE, COLLABORATE!

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While next generation sequencing (NGS) approaches are becoming established in the diagnosis of Mendelian disorders, a critical issue is how to rigorously evaluate novel variants and genes. We report two findings from a research exome sequencing (ES) cohort of patients with epileptic encephalopathy (EE) demonstrating translational research bench-to-bedside and a collaborative approach. First, we report a child of consanguineous parents where ES identified a homozygous single nucleotide change predicted to abolish a splice donor site in the ARV1 gene (c.294+1G>A homozygous). Previously a missense variant (p.(Gly189Arg)) had been reported in ARV1 in one consanguineous family with EE, without supportive functional data. We demonstrate that the c.294+1G>A variant prevents splicing in minigene assays, resulting in exon skipping and an in-frame deletion of 40 amino acids in primary human fibroblasts. Both ARV1 variants result in undetectable levels of ARV1 protein in transfected cells. Mice with a neuronal deletion of Arv1 recapitulated the human phenotype, exhibiting seizures and a severe survival defect in adulthood. Second, we report a child where ES detected a predicted pathogenic de novo missense variant, p.(Phe240Leu), in a novel ion channel gene, KCNT2 (SLICK). Protein modeling was supportive of pathogenicity and electophysiological studies in Xenopus oocytes and mammalian cells demonstrated the variant markedly alters gating properties of the channel in a manner consistent with epileptogenesis. Our data support loss of ARV1 and change in function of KCNT2 as novel causes of EE, demonstrating the importance of collaborations between scientists, clinicians and genomicists to maximise the potential of NGS.

68. A NEW FACE OF COFFIN LOWRY SYNDROME IN FEMALES

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Coffin Lowry syndrome (CLS) is an X linked condition caused by mutations in the RSK2 gene and is characterized by severe intellectual problems, psychomotor retardation, growth retardation and skeletal abnormalities in males and a variable picture in females. Many carrier females of a genetic abnormality for CLS are unaffected and have no features whatsoever. Some have intellectual problems and some can have features as severe as the males with the condition. The known characteristic features of CLS in females include differences in the facial appearance, widely spaced eyes, everted lower lip, developmental delay, learning problems and the characteristic tapering of fingers. However, we have also noticed significant obesity as a presenting feature (in four patients who presented to our clinic), which led to some being investigated for obesity related disorders. We therefore propose inclusion of obesity as one of the important additional feature of CLS in females. It would provide important clue during the diagnostic process for the clinicians and RSK2 gene testing could be offered earlier with subsequent counseling and management as required.

69. WITHDRAWN

70. MATERNALLY INHERITED 15Q DUPLICATION OF UBE3A GENE, WITH ADDITIONAL 47,XXX KARYOTYPE IDENTIFIED BY SNP MICROARRAY

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Cerebral MRI in a 4-year-old girl with moderate global developmental delay, hearing loss and congenital cytomegalovirus infection showed normal inner ears and extensive T2 signal abnormalities within the cerebral white matter (predominantly in the parietal lobes) and cystic changes in the white matter of the temporal lobes anteriorly, consistent with congenital CMV infection. Her mother had intellectual disability, the maternal grandmother and great grandmother were reported to have learning problems. The patient's height weight and head circumference centiles were 25th–75th, she and her 34-year-old mother had no identifiable syndrome, murmurs, neurocutaneous abnormalities, abdominal organomegaly or evidence of skeletal dysplasia. CGH microarray on the girl identified a duplication of chromosome 15q11.2 (25413558-25719127), containing just the UBE3A gene. The patient's mother had a SNP microarray which showed the same duplication of UBE3A, plus a 47,XXX karyotype. *Conclusions:* (1) FISH or array studies of relatives directed just at a region of interest identified in a proband could miss additional findings, such as this mother's triple X karyotype, leading to a misinterpretation of the effects of UBE3A duplication. (2) Congenital CMV infection is common and it is difficult to be certain about its significance in children with neurodevelopmental disorders. One other family has maternal transmission of intellectual disability and/or psychiatric disease associated with a 15q duplication containing just UBE3A (Noor et al., 2015, *Hum Mutat* 36:689-693). Cerebral MRI abnormalities have been reported with deletions of UBE3A but not with duplications, larger ones have been associated with hippocampal and callosal abnormalities.

71. IS A CLINICAL GENETICIST A USEFUL ADDITION TO A PEDIATRIC HEARING LOSS CLINIC?

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Until the development of massive parallel sequencing, the ability to perform genetic testing in non-syndromic, heterogeneous

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conditions such as deafness, was limited. Clinicians had access to testing for connexion 26/30, imaging, and their clinical acumen, which in a small percentage of cases would reveal the diagnosis. Over 80 genes have now been discovered to be the cause of non-syndromic deafness and many other genes to cause syndromic forms of deafness. A molecular diagnosis informs management and reproductive choices. We compared the diagnosis rate prior to clinical genetics (pre-2014) to after a clinical geneticist joined the deafness clinic (post-2014). 88 patients were seen by a single clinical geneticist from 2014 to 2016 with a clinical diagnosis of deafness. Patients were all children seen at a major metropolitan hospital in Melbourne, Australia. Patients had a clinical genetics assessment, and a subset were investigated further with molecular testing. The diagnosis rate by a single pediatrician was 25%, pre-2014. Post 2014, the diagnosis rate with a clinical geneticist was 44% due to increased syndrome recognition and the use of massive parallel sequencing gene panels for diagnosis. Clinical geneticists have a different skill set to pediatricians. They are trained to detect subtle dysmorphic features and recognise rare syndromes, but also to understand and advise on complex molecular testing. These data show that a clinical geneticist embedded in a pediatric hearing loss clinic can significantly increase the diagnosis rate, and thereby improve management and help inform reproductive choices for families.

72. PULMONARY PRESENTATIONS AND OUTCOMES OF NEONATAL AORTOPATHIES — A 20 YEAR REVIEW OF PATIENTS IN VCGS

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Background: A 10-week-old baby presented to the Emergency Department of the Royal Children's Hospital, Melbourne with severe respiratory distress requiring a prolonged hospital admission. He spent 7 days ventilated in ICU requiring high pressures and was difficult to extubate. He was found to have a significantly dilated aortic root and other features of a connective tissue disorder. *Aim:* Pulmonary complications are an unusual presenting feature of neonatal connective tissue disorders. The aims of this project are to characterise the frequency and nature of pulmonary symptoms in neonatal aortopathies, to measure morbidity and mortality of pulmonary pathology and to provide prognostic information in individuals who present with a predominantly pulmonary phenotype. *Methods:* A retrospective chart review of all cases of neonatal aortopathy presenting to RCH over a 20 year period. Cases ascertained by searching the patient databases using keywords: Neonatal, Marfan, Beals, Loeys-Dietz and a date of birth after 1996. *Results:* A total of 16 patients meeting criteria were found. 5 were diagnosed with neonatal Marfan, 4 with Beals and 7 with Loeys-Dietz. Molecular diagnoses were achieved in 7. The most common presenting symptom was a murmur. We found that pulmonary symptoms were an uncommon mode of presentation, but could contribute to the general morbidity of children with neonatal aortopathies. *Conclusion:* Pulmonary complications of neonatal aortopathies are a rare presenting feature of these conditions. When present, these complications confer a significant burden on morbidity and require careful consideration of ventilation requirements.

73. WITHDRAWN

74. ANNUAL AUDIT OF REFERRALS AND CLINIC ACTIVITY OF THE VISITING NORTHERN TERRITORY GENETICS SERVICES

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Background: Since its inception, the supply of specialist clinical genetic services in the NT has undergone considerable change and reorganization. The Victorian Clinical Genetics Services currently oversee the coordination and delivery of clinics at the Royal Darwin Hospital (RDH) and the Alice Springs Hospital (ASH). To date there has been limited available information and understanding surrounding the patients-service interface of this domain. *Aim:* This audit ventured to generate baseline data on the genetics service by summarizing the incoming referrals for a 12-month period and reporting on general clinic activity for the same period. *Methods:* Nominal data were collected retrospectively from the genetics service database located on the NT government health server. Clinic activity information was checked against 'Specialist Outreach NT' reports for accuracy. Primary data will be accompanied by descriptive statistical analysis and visual representations using Microsoft Excel. *Results:* PRELIMINARY results indicate a demand for clinical genetic services, with the number of new referrals for the 12-month period totaling 268 (125 and 249 for the years 2013 and 2014, respectively). Referrals came from diverse range of departments within and outside the NT: Darwin (202), Alice Springs (40), regional areas of NT (16), and interstate (10). In addition to regular telehealth consultations, the service booked a total of 193 face-to-face appointments for RDH (157) and ASH (36). *Discussion/Conclusion:* More research and consumer feedback is required to help further interpret this baseline data, which only begins to describe what has been revealed as a considerable interface of activity with distinct challenges.

GENOMICS

75. WITHDRAWN

76. EMVCLASS: A CLINICAL LABORATORY'S WEB-BASED TOOL THAT FACILITATES VARIANT CLASSIFICATION DIALOG

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Accurate classification of the clinical significance of identified sequence variants is key in genomic medicine. The amount of sequence generated within clinical laboratories has increased dramatically with lower-cost Sanger sequencing and next-generation sequencing technologies. As the number of genes sequenced increases, so does the number of sequence variants identified. Without a mechanism for clinical laboratories to share data, interpretation of sequence variants may be inconsistent. To manage and curate sequence variant data, Emory Genetics Laboratory (EGL) developed a two component data management suite: EmVar and EmVClass. EmVar is a highly curated variant database with a data structure designed to facilitate sharing of information about variants identified at EGL with curated databases. EmVClass is a web-based tool that allows any user access to variants seen at EGL and their current classification. EmVClass has been accessed from 47 states and nearly 80 countries. The data have been downloaded by users, displayed in locus specific databases, and referenced by many studies.

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Being publically available, EmVClass allows users to ask questions, request reviews, and provide comments about variant classification. This interaction allows the laboratory to prioritize review and, if appropriate, update variant classification. In fact, EmVClass inquiries led to reclassification of 16% of variants in question — the majority due to the availability of new information. The dialog benefits healthcare providers as well. Queries from international laboratories are often made when primary literature is not available to them. By providing evidence for our classification, these healthcare providers can have confidence in our assessment.

77. GENE DISCOVERY AND FUNCTIONAL GENOMICS PIPELINE FOR IMPROVED DIAGNOSIS AND TREATMENT IN GENETIC EYE DISEASE

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Blindness due to genetic eye diseases is a significant cause of disability. Genomic medicine presents opportunities to work towards treatments in these conditions where none were previously available. We have developed a discovery and functional genomics pipeline aimed towards improved diagnosis and treatment for patients affected with these disorders. We are applying this pipeline in single gene disorders including retinal dystrophies such as retinitis pigmentosa and glaucomatous eye conditions. We use the tools of genomic medicine including genome engineering, sequencing and stem cell technology for interrogating disease pathophysiology in diseases affecting the retinal pigment epithelium (RPE) and retinal ganglion cells (RGCs). Using genomic approaches and a bioinformatics strategy combining genotype and phenotype information in families and probands with genetic eye diseases, we identified two novel disease-causing genes encoding proteins with roles in cellular signaling and neuronal postsynaptic domains, respectively. We are investigating these proteins using a functional genomics approach encompassing: expression analyses, cell-based assays using shRNA and predicted pathogenic variant transfection, RPE cells or RGCs derived from human induced pluripotent stem cells (hiPSCs) and CRISPR-engineered cell lines and mouse models. The cell-based assays, in conjunction with the mouse models, have provided functional validation of these two disease-causing genes, one critical in centrosomal and ciliary function and the other in Rap signaling. This has led to direct translation to improved diagnostic genetic testing. The hiPSC-RPE and -RGCs and CRISPR-generated mouse models also provide tractable model systems where treatment approaches can be assessed using genetic, cell-based and pharmacological means.

78. DEVELOPING A GENOTYPING PANEL FOR INVESTIGATING AND TREATING GASTROINTESTINAL DYSFUNCTION IN AUTISM

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Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder characterized by a range of social and behavioral indicators. Along with these core signs, individuals with ASD often present with additional medical conditions such as gastrointestinal dysfunction (GID). Signs and symptoms of GID may include abdominal pain, reflux, diarrhoea, and/or constipation. Buie et al. (2010) found that between 9 and 91% of children with ASD presented with GID symptoms. The variety of GID symptoms reported in ASD patients indicates the potential for different subgroups of GID in patients with ASD. To identify these subgroups and gain insights into GID etiology, a targeted genotyping approach was utilized. We have developed a single nucleotide polymorphism (SNP) panel using known SNPs associated with ASD and GID. These SNPSs have been combined with SNPs affecting the efficacy of medications used to treat ASD and associated medical conditions. These combined SNPs were then analyzed using gene-networking mapping to identify genetic links between GID, ASD, and the SNPs that affect medications used to treat ASD. A limited sample of SNPs have now been tested using human DNA extracted from buccal cells to examine the link between GID and ASD. This SNP panel and the data from the DNA samples will be presented, to demonstrate the potential for this panel to be used to confirm, diagnose, subtype, and optimize the treatment of GID symptoms in ASD patients. This study will also aid in the understanding of the mechanism underlying GID in ASD.

79. A CLINICIAN'S APPROACH TO DIAGNOSTIC TESTING FOR GENETIC EYE DISEASES IN THE GENOMIC ERA

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Inherited eye disorders are the leading cause of vision loss in our community. Most of these disorders are characterized by marked genetic heterogeneity. The low yield of traditional sequential single-gene sequencing and its high cost has meant many patients are left without a confirmed diagnosis. Advancements in massive parallel sequencing technology have led to a shift in the diagnostic approach for this group of patients, while the emergence of potential therapies has also driven the impetus for accurate molecular characterization. Here we outline an approach to navigating the various genomic testing options (NGS panel, WES, WGS) available in the clinical setting, where factors such as certainty of diagnosis, limited knowledge of causative genes, test cost and eligibility for research enrolment impact the choice of testing pathway. We also review the utility of this approach in a cohort of pediatric patients who underwent diagnostic testing for a wide range of genetic eye disorders ranging from retinal dystrophy, familial exudative vitreoretinopathy, and developmental eye disease over the last 3 years in the Royal Children's Hospital and Monash Medical Centre multidisciplinary eye genetics clinics in Melbourne. Specifically, we report on variant detection rates by disease category and discuss possible reasons for differing diagnostic rates between these groups, and the demonstrable limitations/benefits of the varying testing technologies. Finally we evaluate the proportion of patients for whom accurate molecular characterization altered clinical diagnosis, or impacted clinical

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management, prognosis, reproductive decision making and eligibility for future therapeutic trials.

80. WITHDRAWN

81. MULTIPLE GENE VARIANTS IN HYPERTROPHIC CARDIOMYOPATHY

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Multiple variants in hypertrophic cardiomyopathy (HCM) were described 13 years ago with small studies suggesting a prevalence of 5% associated with severe phenotypes. With increasing panel sizes, there is limited evidence for greater yield of clinically actionable findings and variants of uncertain significance (VUS) are increasingly reported. We sought to re-examine the significance of multiple variants in the era of panels. Probands with HCM and $\geq$ 46 genes sequenced were included. Rare variants (allele frequency $\leq$0.0002) within 46 cardiomyopathy genes were analyzed. Variants were classified using modified American College of Medical Genetics criteria. 340/726 probands (47%) had 46 genes sequenced. 203 (60%) had $\geq$ 1 variant, with 87 (43%) variants in non-HCM genes. Prevalence of multiple variants was 17% in 46 genes, 5% in 15 genes, 3% in 8 genes, 2% in 5 genes. Yield of identifying likely pathogenic/pathogenic variants did not increase with increasing panel size beyond the top 8 genes (33% when considering 46 genes, 32% when considering 5 genes and 28% in MYBPC3 and MYH7). The frequency of VUS increased from 11% in 2 genes to 37% in 46 genes. No proband with multiple variants had two pathogenic/likely pathogenic variants. Single variants were more likely to be in the top 8 HCM genes (92% vs. 73%, $p = .01$), have lower allele frequencies (0.000005 vs. 0.00001, $p = .03$) and be classified likely pathogenic/pathogenic (65% vs. 15%, $p < .0001$). The likelihood of identifying multiple rare variants when using large panels is high, though these variants may be less deleterious.

82. GENOMICS AND THE RETINAL DYSTROPHIES

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Genomic approaches to genetic diagnosis are valuable in conditions with high clinical and genetic heterogeneity. The retinal dystrophies (RD) are degenerative disorders of the retina affecting both rod and cone photoreceptors. They affect approximately 1/3500 people and prioritizing the >200 known causative disease genes is challenging. Currently there is no clinical diagnostic testing available for RD in Australasia which allows for the examination of all the known genes in a cost effective and timely manner. We are using a number of next-generation sequencing (NGS) strategies in RD patients to determine their relative value. In a cohort of 36 patients with familial or sporadic RD, we utilized the Illumina TruSight One targeted exome panel. Subsequently libraries were sequenced on the Illumina HiSeq 2500. Variants detected in the 217 RD genes of interest were filtered and prioritized on in silico allele frequencies, conservation and pathogenicity prediction scores, with final candidate variants categorized using ACMG guidelines. Novel and previously reported frameshift, missense and premature stop mutations were identified in several genes including the syndromic genes BBS1, USH2A and IFT140. Molecular diagnosis was achieved in 23/36 (64%) families allowing for improved patient management and recurrence risk information. Furthermore, in specific cases the use of panel-based testing facilitated a change in clinical diagnosis to another type or syndromic form of RD. The application of our NGS strategy has been successful in identifying pathogenic variants in the heterogeneous RDs, while also integrating with existing bench work processes for NGS testing already being performed by the laboratory.

83. FULL MITOCHONDRIAL GENOME SEQUENCING IN RELATION TO MIGRAINE IDENTIFIES A NOVEL MUTATION IN TRNA TRYPTOPHAN IN THE GENETICALLY ISOLATED NORFOLK ISLAND POPULATION

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Background: The genetically isolated Norfolk Island population is an ideal cohort for the identification of genetic variation contributing to complex disease as genetic and environmental heterogeneity is reduced. Symptoms of mitochondrial diseases include severe migraine attacks which has led researchers to hypothesize that mitochondrial dysfunction may be linked to the more common subtypes of migraine. *Methods:* The aim of this study was to provide a comprehensive molecular genetic approach to fill a significant knowledge gap in the field where previous studies have been limited by sample size by investigating whether mitochondrial genetic variation is associated with migraine susceptibility. A custom developed in-house methodology was used to undertake whole mitochondrial genome sequencing on all of the Norfolk Island individuals within the core pedigree. *Results:* Logistic regression modeling showed that one common variant mt.189 A>G located within the mitochondrial hypervariable region is nominally associated with migraine ($p = .04208$). In additional to this finding 8 homoplasmic rare variants and 1 heteroplasmic common variant were found to also be nominally associated with migraine susceptibility. Importantly a novel potentially damaging mutation was identified in a migraineur within the tRNA tryptophan t stem functional domain. *Conclusion:* This study has identified a novel mutation m.5558 A>G (tRNA trp) in an affected migraine sufferer, indicating a possible role for this mutation in relation to migraine. Several mitochondrial variants were also found to be nominally associated with migraine susceptibility, some within genes involved in OXPHOS function, suggesting an important role for OXPHOS in migraine susceptibility.

84. A NOVEL GENETIC CAUSE OF X-LINKED PAEDIATRIC CATARACTS IN AN AUSTRALIAN FAMILY

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Background: Pediatric cataracts are a leading cause of childhood blindness and the genetic heterogeneity complicates a molecular diagnosis. A novel locus for X-linked pediatric cataracts in an 11.5Mb region at Xq24 was previously reported for an Australian

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family; however, the causative mutation remains to be identified. *Hypothesis:* To refine the Xq24 linkage region and identify the causative mutation in the family. *Methods:* Genome-wide parametric linkage analysis was performed using Illumina® HumanOmniExpressv1.1 SNP array data to confirm and refine X chromosome linkage and to assess the remainder of the genome for linkage. A Complete Genomics™ whole genome sequence of an affected individual was used to identify candidate variants which were validated and assessed for segregation using Sanger sequencing. *Results:* A 6.8Mb linkage region, between rs2428312 and rs7887767, was confirmed at Xq24 (LOD = 2.53). A 127kb deletion was the only segregating variant identified within the linkage region and causes the removal of an uncharacterized long non-coding RNA gene LOC101928336 and truncation of the PGRMC1 gene following exon 1. Two additional regions suggestive of linkage at 1q43 and 3q26 (LOD = 2.48) remain to be investigated for potential disease causing variants. *Discussion:* The likely cause of pediatric cataracts in this Australian family is the 127kb deletion at Xq24. Neither of the two genes impacted by this deletion have previously been associated with cataracts indicating a novel genetic cause. These findings will facilitate genetic counseling for asymptomatic female carriers within the family and can facilitate further study into cataract disease mechanisms.

85. MOVED TO ORAL PRESENTATION — ORAL 7

86. RARE VARIANTS IN COL5A1, FOXO1 AND CAST ARE LIKELY TO CONTRIBUTE TO KERATOCONUS DEVELOPMENT, A BLINDING EYE DISEASE.

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Keratoconus is a complex eye disease with a strong genetic basis in which the cornea progressively thins and protrudes, resulting in severe visual impairment. Many candidate genes have been suggested based on gene function, family studies and proximity to genome-wide association hits. We sequenced 19 candidate genes in 349 Australian keratoconus patients on a MiSeq (Illumina) using a custom HaloPlex target enrichment (Agilent). SureCall (Agilent) was used to align reads to hg19 and call variants. Potentially pathogenic variants were classified as those with a minor allele frequency <1% in the non-Finnish European ExAC population that were either predicted to be damaging by SIFT or PolyPhen2, or were nonsense variants. For each gene, chi square or Fisher exact tests were used to compare the number of variants between cases and a control cohort consisting of 993 Australians with whole exome sequencing data (sequenced using the TruSeq exome enrichment on an Illumina HiSeq and variant calling using the GATK pipeline). No potentially pathogenic variants were identified in cases in IMMP2L, RAD51, SOD1, IL1B or IL1RN. No enrichment of variants was identified in cases in BANP, MPDZ, RAB3GAP1, HGF, FNDC3B, NFIB, COL4A3, COL4A4, TF, IL1A, or SLC4A11 and therefore rare coding variants in these genes are unlikely to contribute to disease. Nominally significant association was identified in COL5A1 ($p = 0.011$, *OR* 2.0 [1.2–3.5]), FOXO1 ($p = .018$, $OR = 4.0$ [1.1–14.6] and CAST ($p = .017$, $OR = 3.5$ [1.2–10.1]), demonstrating that rare coding variants in these genes may be involved in keratoconus and warrant further investigation.

MOLECULAR GENETICS

87. INVESTIGATION OF THE FUNCTION OF NOVEL RETINAL DYSTROPHY DISEASE GENES

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Retinal dystrophy describes progressive degeneration of photoreceptors (rods and cones) leading to vision loss, with a worldwide prevalence of approximately 1 in 3500. Many of the underlying disease genes and their functions are not known. In a family with an inherited novel syndromic retinal dystrophy, we undertook genomic and cell-based approaches to identify and understand the function of the novel disease gene. Affected family members showed signs of retinal dystrophy with abnormal retinal lamination. Genomic and bioinformatics analyses revealed a missense mutation in a novel candidate disease gene with a high pathogenicity prediction score, absence in ExAC and appropriate segregation. Expression analyses showed presence of the protein in the retinal pigmented epithelium and inner segments of the photoreceptors. Immunocytochemical studies in HeLa cells and human fibroblasts showed localization of the protein in the spindle poles during mitosis and midbody of the intracellular bridge in cytokinesis. In serum starved primary human fibroblasts we observed expression of the protein in the basal body of the cilia. Patient fibroblast cells showed abnormal numbers of centrosomes in mitosis and at interphase. In this study, using genomic and phenotype-based bioinformatics approaches in retinal disease, we identified a novel syndromic retinal dystrophy disease gene. Our expression and functional studies have shown the role of this gene in cell cycle, signaling and proliferation. These findings provide validation of the candidate as a retinal dystrophy disease gene, and insight to the pathophysiology of the disease, paving the way for development of therapeutic strategies in the future.

88. X-LINKED CLCN5 VARIANTS IN A MULTI-GENERATIONAL FAMILY WITH VARIABLE AGE-OF-ONSET OF RENAL FAILURE AND PROTEINURIA

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Background: Pathogenic variants in the CLCN5 gene are associated with Dent Disease, a rare, X-linked disorder of renal tubule function that classically results in pediatric presentation of hypercalciuria, stones, nephrocalcinosis and renal failure. We report a case of an extended family with a likely pathogenic CLCN5

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variant with variable age of onset of renal failure, with no history of hypercalciuria or stones. *Case Report:* Pedigree analysis revealed a large, multi-generational family, with seven males affected with chronic kidney disease (5 with renal failure and 1 with chronic impairment). There are no affected females. All had low-range proteinuria without history of hypercalciuria or stones. Five of the seven presented in childhood; however one presented in their third decade of life and another in their sixth. Four of the patients underwent renal biopsy, which demonstrated some diffusely sclerosed glomeruli, patchy interstitial fibrosis and chronic inflammation. Two affected brothers were investigated via whole exome sequencing. A novel missense variant was identified in CLCN5 (NM_001127899.3:c.933G>C:p.Glu311Asp). This variant segregated among affected family members across several generations, and was thus classified likely pathogenic. Another family member with normal phenotype was not found to carry the familial variant, and was thus able to be assessed as a living kidney donor. *Conclusions:* We describe an extended phenotype of this rare X-linked disorder. This case highlights the benefits of NGS to broaden the phenotypic knowledge of previously described disorders and the benefits of pursuing a molecular diagnosis that has had implications for clarification of diagnosis, management, transplantation and family-planning.

89. ANALYSIS OF THE PIGMENTATION PATHWAY IN A FAMILY WITH TIETZ SYNDROME DUE TO A MUTATION IN THE MITF GENE — FURTHER EVIDENCE OF DIGENIC INHERITANCE?

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Tietz syndrome (TS) is an autosomal dominant disorder of congenital sensorineural hearing loss and generalized hypopigmentation due to a heterozygous mutation in the MITF (microphthalmia-associated transcription factor) gene. The MITF gene encodes a transcription factor involved in the development of pigmentary cells in the retina, inner ear and skin. Mutations in MITF are responsible for Waardenburg syndrome type 2a and variants: WS2 with ocular albinism (WS2/OA) and TS. One proposed model for the variation in pigmentation seen in WS2/OA and TS is digenic inheritance of a MITF mutation with a second mutation of a downstream target. Two candidate genes have been reported in families with WS2/OA: TYR and TYRP1. Molecular and phenotypic characterization of families with WS2/OA or with TS will aid further delineation of the pigmentation pathways. We present a family of four children, three of whom have congenital profound sensorineural hearing loss in association with striking blue irides, iris transillumination defects, fundal hypopigmentation and variable skin pigmentation consistent with TS. In addition, the proband presented with bilateral colobomas, in the absence of microphthalmia. Biallelic MITF mutations have been previously reported in patients with colobomatous microphthalmia, macrocephaly, albinism and deafness (COMMAD syndrome). Genetic testing of the proband, using a commercially available pigmentation panel, detected a pathogenic heterozygous mutation in the MITF gene together with a number of variants in candidate pigmentation genes, including an OCA2 and TYRP1 variant. Family studies from both affected and unaffected individuals will be presented.

90. NOVEL GENE IDENTIFICATION AND FUNCTIONAL CHARACTERISATION IN MICROPHTHALMIA, ANOPHTHALMIA, COLOBOMA (MAC)

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Background: Microphthalmia, anophthalmia and coloboma (MAC) are congenital anomalies of the eye leading to small or absent eyes associated with failure of closure of the optic fissure. Variants in a number of genes including SOX2, OTX2, CHX10, BMP4 and RAX, contribute to the MAC phenotype. However, the majority of the disease-causing genes are yet to be identified. Variable penetrance and expression are among the factors impeding the disease gene identification process. *Aim:* Delineate disease-causing variants in families with MAC, and undertake cellular functional characterization of the variants. *Methods:* We employed whole exome sequencing (WES) in affected members of two autosomal dominant MAC families. No mutations in known disease genes were identified. Bioinformatic analysis incorporating variant prioritization and a phenotype-driven approach, led to strong candidate disease gene identifications in both families. The mutations were cloned into GFP expressing vectors and subjected to functional analysis. Comparative analysis of cellular location was performed upon overexpression of the mutant and wild type genes in HEK293 cells. Luciferase assays were used to interrogate the impact of the identified mutations on the corresponding signaling pathways. *Results:* We identified two novel variants segregating with the disease phenotype in two genes not previously known to be associated with MAC. Alteration of cellular location in HEK293 cells was identified upon overexpression of one of the mutated genes. Luciferase assays demonstrated abnormal levels of activation of the corresponding reporters. *Conclusion:* Our findings demonstrate the role of two newly identified genes contributing to the MAC phenotype.

91. 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 4 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 which 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

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of test requests. We continue to look at ways to streamline testing despite a geographically dispersed physical laboratory structure.

92. NADPH OXIDASE 4 (NOX4) DEFICIENCY: THE SCAD 'DEFICIENCY' REVISITED?

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Background: NOX4 encodes NADPH Oxidase 4, an enzyme that functions as the catalytic subunit of the NADPH oxidase complex. NOX4 acts as an oxygen sensor, catalysing the reduction of molecular oxygen, mainly to hydrogen peroxide (H2O2). *Aim:* To identify the genetic basis of an unusual clinical phenotype in an infant and provide pre-implantation genetic diagnosis (PGD) options. *Patients & Methods:* The proband had a lethal phenotype of respiratory distress, failure to thrive, pancreatic insufficiency, liver dysfunction, hypertrophic cardiomyopathy, bone marrow suppression, humoral and cellular immune deficiency. A trio whole exome sequencing (WES) was used followed by structural and functional studies of fibroblast extracts. *Results:* We identified a homozygous novel variant, c.6_7insGAG (p.Glu3dup), in NOX4 in the proband, and parental heterozygosity (confirmed by Sanger sequencing). Immunoblotting in patient fibroblast extracts showed reduced NOX4 protein levels. There was a 75% reduction in the production of H2O2 compared to controls. Gene rescue studies are in progress. Karyomapping was chosen for PGD, however; two of the grandparents shared the proband's homozygous genotype. One of the grandparents had fibromuscular dysplasia. Bioinformatic databases have now disclosed a high allele frequency. *Conclusion:* Mendelian diseases are reported in the NOX family, and NOX4 was an attractive candidate gene in our patient, strengthened by the functional data. Our case highlights a potential pitfall associated with the shifting bioinformatics data in WES. The strong functional data suggested a disease process, but draws similarity to the SCADD story, where functional defects in fatty acid oxidation have variable if any clinical ramifications.

93. PROTOCADHERIN 19 (PCDH19) REGULATES ESTROGEN RECEPTOR ALPHA (ERA) THROUGH PARASPECKLE PROTEIN NONO

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PCDH19 girl clustering epilepsy (GCE) is a frequent, early-onset neurodevelopmental disorder of highly variable epilepsy, intellectual disability, autism and behavioral problems. Intriguingly, hemizygous null males are not affected while heterozygous females are, contradicting established X-chromosome inheritance. The disease mechanism is not known. Cellular mosaicism is the likely driver. We have identified p54nrb/NONO, a multifunctional nuclear paraspeckle protein with known roles in nuclear hormone receptor gene regulation, as a PCDH19 protein interacting partner. Based on the altered gene expression in PCDH19-GCE skin fibroblasts, we postulated that PCDH19 protein might regulate estrogen receptor alpha (ERα). NONO and estrogen signaling is crucial for normal brain development. Using breast cancer cell lines MCF-7 and MDA-MB-231, expressing, or not expressing endogenous ERα, respectively, we demonstrated that PCDH19 protein is a positive regulator of ERα-mediated gene transcription. Importantly, this PCDH19 protein activity is enhanced by NONO and abolished when different PCDH19-GCE mutations were tested. These findings are consistent with the PCDH19-GCE patient skin fibroblast expression studies, where known targets of nuclear hormone receptors were dysregulated. Overall we define and characterize a novel mechanism of gene regulation driven by the cell adhesion molecule PCDH19, which is mediated by paraspeckle constituent NONO and is ERα dependent. This novel PCDH19-NONO-ERα axis is of relevance to GCE and potentially to other neurodevelopmental and behavioral disorders. This work will enhance our understanding of the mechanism of disease as well as provide opportunities for improved diagnosis and treatment with existing pharmacotherapies that target estrogen.

94. FAMILIAL HYPERCHOLESTEROLEMIA: A RARE CASE REPORT OF HOMOZYGOUS LDLR MUTATION DETECTED IN INDIAN FAMILY

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Background: Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder with a prevalence of 1 in 500. Mutations have been found in 3 genes: LDLR, APOB and PCSK9. Early identification of FH in patients and screening of first degree relatives are recommended to minimize the risk for premature CHD. *Aim:* In this study, we screened for mutations in LDLR gene in an Indian family, where FH was detected in the index patient using NGS. *Methods:* Targeted gene sequencing involving selective capture and sequencing of the protein coding regions of the genes was done in order to identify mutations in FH implicated genes. The libraries were sequenced to mean >80-100X coverage on Illumina sequencing platform. Sequences obtained were aligned to the GRCh37/hg19 human reference genome and clinically relevant mutations were annotated using published variants. The mutation identified in the index patient was validated by Sanger sequencing. Parents and sibling were screened for this mutation using Sanger sequencing. *Results:* p.D90Y mutation was identified in the LDLR gene in homozygous condition in the index patient. The parents were found to be heterozygous and the sibling homozygous for this mutation. This variant is predicted to be damaging by SIFT and Mutation taster and this region is conserved across species. *Conclusion:* Here, we present a very rare case (1 in a million) of p.D90Y mutation detected in homozygous condition. Not many studies have been carried out in Indian cohorts and we plan to further investigate the genetic aspects of FH in Indian subjects.

CYTOGENETICS

95. RMI2, A NEW BLOOM'S SYNDROME GENE

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The BLM Bloom's syndrome gene was first identified over 20 years ago. The BLM protein is a DNA helicase that is part of the BTR complex which dissolves double Holliday junctions to prevent genome instability. Here we report the first clinical case of patients with

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homozygous mutations in the RMI2 subunit. This is the first clinical description of a non-BLM subunit. Two affected children have some clinical features that are characteristic of Bloom's syndrome. Microarray screening revealed an 80 kb deletion completely spanning the RMI2 gene. To further confirm that the affected children had cytological features of Bloom's syndrome we performed sister chromatid exchange (SCE) assays and observed the behavior of chromosomes during cell division. Each affected child showed a 7 to 8-fold increase in the rate of exchange events when compared to parental controls. Furthermore, cells observed in anaphase displayed DNA bridges and an elevated frequency of micronuclei. To independently support the findings observed from the affected children and to further support our cell biology analyses, we disrupted the RMI2 gene in the near-diploid cell line, HCT-116, using CRISPR/Cas9 gene-editing. In three independent knockout clones we observed similar cytogenetic phenotypes such as, higher rates of SCEs, slower cellular proliferation, and DNA fibres during anaphase. BLM partner proteins localise to the DNA fibres, but are present at lower levels when compared to wild type cells. We conclude that RMI2 mutations lead to Bloom's syndrome-like characteristics both at the patient and the cellular level.

96. WITHDRAWN

97. WITHDRAWN

98. STRUCTURAL AND COPY NUMBER VARIATION DETECTION FROM HISEQ X WHOLE GENOME SEQUENCING DATA

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Genomic structural variation (SV) including copy number variation (CNV) underlies the etiology of many human genetic disorders and syndromes. Clinical microarrays have been the mainstay of diagnosing CNVs in patients; however, they are of limited use in detecting inversions, translocations and small CNVs. The rapidly decreasing cost combined with the broad and uniform depth of coverage from Illumina HiSeq X whole genome sequencing (WGS) data presents a unique opportunity to improve detection of CNVs and SVs across the entire size gamut from a few nucleotides, to entire chromosomes, in a clinical setting. We have developed a pipeline for detection, annotation, filtering and visualization of SV. By complementing changes in read depth with split-reads and discordant-reads, we often resolve the precise SV breakpoint, and smaller events than using depth alone. We identify on average 5500 SV per patient, where only ~40 are rare (<1%) and overlap genes. We have validated the method extensively, through comparison to NA12878, and patients with clinical microarray data. Sensitivity is >90%, with some difficulty at resolving short tandem repeats in the 200–500bp size range, due to repeats that are longer than the reads. Reproducibility between runs is generally >80%, and higher for deletions that are not associated with ancient segmental duplications (>90%). Note that performance substantially improves following manual review of any discordant calls, which is essential for SV calling, as repetitive reference sequence leads to incorrectly mapped reads. We will present our findings from applying these methods to dilated cardiomyopathy, renal-, mitochondrial- and movement-disorders.

99. A RARE RECIPROCAL INSERTION AND TRANSLOCATION IN A FEMALE WITH SHORT STATURE

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The observation of two unrelated balanced rearrangements in peripheral blood is a rare occurrence. A balanced reciprocal translocation has a frequency of 1:500 live births, making it one of the most common chromosomal rearrangements that can occur. However, an interchromosomal insertion is an extremely rare phenomenon with an estimated frequency of 1:80,000 live births. The proband presented at nine years of age as a female with short stature and no other clinical information. Cytogenetic G-banded analysis and fluorescence in situ hybridization (FISH) revealed the following karyotype: 46,XX,t(7;14)(q34;q11.2),ins(17;2)(q23.3;q35q?37.2).ish ins(17;2)(wcp2+D2S447+).

Parental chromosome studies are recommended to determine if these rearrangements are inherited or de novo mutations. If these changes have not been inherited then they are more likely to be associated with a phenotypic effect. The complex nature of this karyotype is also a factor in assessing the likelihood of the rearrangement being associated with the phenotype. An array is also recommended to determine if there has been any loss or gain of material at the breakpoints. Genetic counseling is recommended for this case. This case report demonstrates a cytogenetic finding of two unrelated rearrangements which is of particular interests both for its implications for the proband and for its rarity.

100. ELUCIDATION OF MICROARRAY FINDINGS USING TRADITIONAL KARYOTYPING: A CASE STUDY INVOLVING 15q11q13 TETRASOMY

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In recent years, chromosomal microarray has become the most common test performed in clinical cytogenetics. While this has allowed access to more genomic information than ever before, microarray data does not always tell the full story, and more traditional cytogenetic techniques still have their place. In this case study, a 21-week gestation amniotic fluid was received by the lab for abnormal ultrasound findings including intracardiac echogenic focus, bilateral choroid plexus cyst, and bilateral superior vena cava. While routine rapid aneuploidy screen was normal, microarray results showed a 12Mb copy number gain of 15q11q13. The array profile was suggestive of triplication, encompassing the region associated with Prader-Willi and Angelman syndromes. Confirmation with traditional karyotyping and metaphase FISH, however, led to the discovery of two cell lines — one with a normal male karyotype, and one with an additional two markers derived from chromosome 15. Parental microarrays were normal, indicating a de novo event. The relative complexity of this karyotype was only uncovered by using traditional cytogenetic techniques as an adjunct to chromosomal microarray.

101. PLASMA CELL (CD138+) ENRICHMENT USING TWO DIFFERENT KITS — MACS VERSUS EASYSEP: A VALIDATION STUDY

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Background: Multiple myeloma (MM) is a plasma cell (PC) neoplasm in which the surface antigen CD138 (syndecan-1) is

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expressed at high levels. In our laboratory, we previously showed FISH gives higher abnormalities rates on uncultured CD138+ enriched cells compared to routine cultured cells (50.8% vs. 7.4%, $p < .001$], using a probe panel for t(11;14), 13q and 17p loss. Enriched plasma cells are also used for chromosome microarray analysis. CD138+ enrichment subsequently became standard laboratory practice, however the process can be time consuming. *Aim:* We evaluated FISH abnormality rates and processing time using two commercial kits for enrichment of CD138+ PCs. Method: Fourteen bone marrow samples were enriched in parallel using two different commercial kits, according to manufacturer instructions. These included the EasySep Human Pan-B (STEMCELL Technologies) and MACS whole Blood CD138 MicroBeads human (Miltenyi Biotec) kits. Sample processing times and different FISH abnormality rates were compared using the paired-means t-test with a significance level $\alpha = 0.05$. *Results:* The FISH abnormality rate for the MACS vs EasySep kit was 80.8% vs 76.9%, which was marginally higher at 4% but was not statistically significant ($t = 2.17$, $df = 13$, $p = .049$). The processing time was 0.5 versus 2 hours, respectively. *Conclusion:* There was no difference in FISH abnormality rates between the MACS whole Blood CD138 MicroBeads kit vs the EasySep kit but the MACS kit was a quicker and less labour intensive technique for PC enrichment. However, the MACS kit is more expensive.

102. UTILIZATION OF NON-INVASIVE PRENATAL TESTING TO EXCLUDE AN UNBALANCED KARYOTYPE IN A TRANSLOCATION CARRIER'S PREGNANCY: A CASE STUDY

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This case study illustrates the innovative use of cell free DNA technology for prenatal testing for a 27-year-old balanced translocation carrier. The patient, G8P0 had recurrent first trimester miscarriages, and was discovered to carry a 13;16 balanced reciprocal translocation: t(13;16)(q14.1;q22.3). She attended genetic counseling to discuss the potential prenatal testing options. The patient and her husband declined invasive testing for prenatal diagnosis, due to the associated miscarriage risks. Given the two chromosomes involved in her translocations were both being analyzed using cell free DNA technology in Australia at the time, the US based laboratory (Sequenom®) were able to report whether they detected any copy number variants around the specific translocation breakpoints. The patient was counselled that this testing was not diagnostic, but rather utilized as an adjunct screening method with ultrasound, in lieu of invasive prenatal diagnosis. The report indicated no abnormalities, confirmed postnatally to be a 46,XX karyotype. Requests to use cell free DNA for assessment of chromosomes other than 21, 18, and 13 have increased over time. To meet this need, MaterniT^{TM}GENOME, a whole-genome cell free DNA test, was developed for patients known to be at-risk for chromosome anomalies other than the common trisomies. This laboratory-developed test (LDT) is able to identify chromosome gains and losses (suggestive of unbalanced translocations) $\geq$7 Mb and becomes another tool available to clinicians in prenatal risk assessment. We believe patients with balanced reciprocal translocations could benefit greatly by further development and accreditation of NIPT technology for this purpose in Australia.

103. AN UNLIKELY EXPLANATION: TWO ABNORMAL PREGNANCIES LEAD TO THE CONCLUSION THAT THE CLIENT IS THE RESULT OF A TRISOMY RESCUE.

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We present a case with evolving complexity over two pregnancies. Our client (30 years) presented in her first pregnancy at 12 weeks with an increased risk on first trimester combined screening. Chorionic villus sampling (CVS) was performed and the FISH result indicated trisomy 21. The chromosome microarray (CMA) confirmed trisomy 21 and detected a novel 4MB microdeletion on one of the chromosome 21 copies. The couple elected to have a termination of pregnancy. Subsequent investigations were normal (parental CMA and parental FISH for the chromosome 21 microdeletion). In her second pregnancy, our client elected to have non-invasive prenatal screening initially, which was low risk. However, the 12 week scan was abnormal. CVS was performed and the FISH result was normal. CMA detected the same chromosome 21 microdeletion seen in the previous pregnancy, indicating partial monosomy 21 in this fetus. The second pregnancy revealed that gonadal mosaicism for the chromosome 21 microdeletion was present. Further investigations led to the unlikely conclusion that the client is the result of a 'trisomy rescue'. We will discuss our management of the case, including the investigations performed and the genetic counseling issues raised.

BIOCHEMICAL GENETICS, NEWBORN SCREENING AND DIETETICS

104. THE INFLUENCE OF A COMMON GENETIC VARIANT (ACTN3 R577X) ON THE OSTEOCALCIN RESPONSE TO ACUTE HIGH-INTENSITY EXERCISE IN YOUNG HEALTHY MALES

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Background: Osteocalcin (OC) is a marker of bone formation, while the undercarboxylated form of OC (ucOC) modulates insulin sensitivity. Exercise increases serum ucOC levels, however, there is large variation between individuals. This variation is potentially influenced by the presence (RR and RX genotypes) or absence (XX genotype) of α-actinin-3 protein (ACTN3 R577X common variant), as the protein is expressed in osteoblasts, bone cells that secrete OC and ucOC. *Aim:* To examine whether the ACTN3 R577X influences changes in OC and ucOC pre-and-post exercise. *Methods:* Forty-four healthy Caucasian individuals (Age: 30.1±1.4 years, BMI = 25.5±0.4 kg×m-2) were divided into three groups (ACTN3XX, $N = 13$; ACTN3RX, $N = 16$; ACTN3RR, $N = 15$). Participants completed a single session of High Intensity Interval Exercise (HIIE) on a cycle ergometer (8×2-min intervals at 85% of maximal power with 1 min of recovery between intervals). Blood samples were taken before, immediately after, and three hours post exercise to identify the peak change in OC and ucOC. *Results:* At baseline, XX individuals had a higher OC level compared to their RR counterparts (37.3±3.9 vs. 28.2±1.7 ng/mL, $p = .04$). ucOC was similar across genotypes (all $p > .37$). Following HIIE, OC levels increased only in RX individuals (9%, $p = .001$), whereas ucOC level increased in all three groups (XX ˜8%, $p = .02$; RX ˜11%, $p = .006$ and RR ˜7%,

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$p = .08$). *Conclusion:* Individuals with ACTN3 XX variation are characterized by a higher circulating levels of OC, which may indicate a higher bone remodeling compared to RR individuals. The response of ucOC to exercise is not explained by ACTN3 R577X.

105. MUTATION DETECTION FOR BIOCHEMICAL GENETICS IN THE GENOMIC ERA

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Introduction: There is an increasing requirement to confirm the enzyme or analyte diagnosis of a biochemical genetic disorder by molecular genetic testing. The introduction of next generation sequencing into our laboratory has enabled cost-effective molecular testing with improved turn-around time. In order to further increase efficiency and reduce costs, we have created a customized panel of 77 common mutations in 29 biochemical genetic disorders for 'first-tier' testing to reduce the number of mutation searches required. *Method:* A MassArray Primer Extension custom panel was designed by Agena Bioscience. The 77 common mutation panel is divided into 3 multiplexed assays. Testing involves an initial PCR step, shrimp alkaline phosphatase step (removes residual dNTPs) followed by a primer extension step before spotting onto a SPECTRAchip. Analysis is performed on a MALDI-TOF where single base primer extension products are separated based on mass. The panel is being validated using known patient samples. *Results:* A patient homozygous for a common PEX1 gene mutation (peroxisomal biogenesis disorder) was detected in our initial run and confirmed with parental samples. Issues of false negative and positive results due to underlying SNPs at the primer binding sites have required redesign of some assays. *Conclusion:* This panel gives us the ability to combine mutation testing for multiple disorders in a single, flexible workflow that handles both low and high throughput testing. Applications include rapid common mutation screening, familial mutation analysis and prenatal testing.

106. MUCOPOLYSACCHARIDOSIS IVA (MORQUIO A SYNDROME): A DIAGNOSTIC CHALLENGE

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Mucopolysaccharidosis (MPS) IVA (Morquio A) is an autosomal recessive lysosomal storage disorder (LSD) that arises due to the deficiency of N-acetylgalactosamine 6-sulphatase (GALNS) activity. Two glycosaminoglycans (GAGs), chondroitin 6-sulphate (CS) and keratan sulphate (KS), accumulate in tissues, bones, and major organs and are excreted in urine. Diagnosis can be difficult, particularly in patients with an attenuated phenotype. We present two MPS IVA siblings to illustrate the diagnostic challenges of MPS IVA. Sibling 1 (male, born 2003) presented at 7 years of age with occasional knee pain and was found to have generalized bone dysplasia on X-ray. Sibling 2 (female, born 2004) presented with short stature. LSDs were investigated in 2010, with urinary GAG electrophoresis and lysosomal enzyme studies both yielding normal results for the siblings. From 2010–2015 the siblings were classified as having an unspecified type of spondyloepiphyseal dysplasia (SED). As clinical suspicion of MPS IVA persisted, repeat urinary GAG analysis and GALNS enzyme analysis were performed in 2015. Sibling 2's urinary GAG electrophoresis yielded a pattern consistent with MPS IVA, with KS present. Her GALNS activity (9.6 nmol/17h/mg; RR 96–360) was also markedly reduced. While also displaying markedly reduced GALNS activity (14 nmol/17h/mg), Sibling 1's GAG electrophoresis pattern was normal. Molecular studies of their GALNS gene confirmed the diagnosis of MPS IVA. This case highlights the challenges in diagnosing MPS IVA patients. GALNS activity should always be analyzed if there is clinical suspicion of MPS IVA.

107. CARDIAC INVOLVEMENT IN GENOTYPE-POSITIVE FABRY DISEASE PATIENTS ASSESSED BY CARDIOVASCULAR MR: AN AUSTRALIAN COHORT

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Background: Cardiac magnetic resonance (CMR) has the potential to provide early detection of cardiac involvement in Fabry disease. *Aim:* To gain further insight into this by assessing a cohort of Fabry patients using CMR. Methods/results Fifty genotype-positive Fabry subjects (age 45±2 years; 50% male) referred for CMR and 39 matched controls (age 40±2 years; 59% male) were recruited. Patients had a mean Mainz severity score index of 15±2 (range 0–46). Compared with controls, Fabry subjects had a 34% greater left ventricular mass (LVM) index (82±5 vs. 61±2 g/m2, $p = .001$) and had a significantly greater papillary muscle contribution to total LVM (13±1 vs. 6±0.5%, $p < .001$). Late gadolinium enhancement (LGE) was present in 15 Fabry subjects (9/21 males and 6/23 females). The most common site for LGE was the basal inferolateral wall (93%, 14/15). There was a positive association between LVM index and LGE. Despite this, there were two males and three females with no LVH that displayed LGE. Of Fabry subjects who were not on enzyme replacement therapy at enrolment ($n = 28$), six were reclassified as having cardiac involvement (four LVH-negative/LGE-positive, one LVH-positive/LGE-positive and one LVH-positive/LGEnegative). *Conclusions:* CMR was able to detect cardiac involvement in 48% of this Fabry cohort, despite the overall mild disease phenotype of the cohort.

108. PARENTAL ATTITUDES TO USING WHOLE GENOME SEQUENCING IN NEWBORN SCREENING PROGRAMS IN AUSTRALIA

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Background: Whole genome sequencing (WGS) is increasingly being included in medicine for diagnostic purposes due to decreasing costs and turnaround times. Internationally, WGS is also being considered for newborn screening (NBS), as it has the potential to screen more conditions than currently included. However, results can be difficult to interpret, conditions may not be amenable to treatment and/or will not onset until adulthood. *Aim:* To determine the knowledge of Australian parents regarding current NBS and their attitudes towards incorporating WGS. Based on international

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findings, it is hypothesized that the majority will be in favour of WGS, but not at the expense of current methods. *Methods:* Parents who may have recently experienced NBS will be invited via social media, parenting newsletters and the NSW NBS program consumer list to complete a brief anonymous online questionnaire (modified from a Canadian study (Bombard et al., 2014 *Eur J Hum Gen,* 22: 1248–1254). Survey items include participant knowledge of the current NBS program, attitudes to the use of WGS in NBS, and possible information and support needs if new technologies were to be introduced. Data will be compared to the findings of the Canadian study. *Significance:* The benefits of NBS can only occur if the majority of parents' elect not to 'opt out' of screening. For this reason, gauging parental understanding of the current NBS program and attitudes towards potential changes to NBS is vital in maintaining the success of future programs.

109. ATTITUDES OF HEALTH PROFESSIONALS TOWARDS INCORPORATING WHOLE GENOME SEQUENCING INTO NEWBORN SCREENING IN AUSTRALIA

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Introduction: As whole genome sequencing (WGS) in the clinical setting becomes a reality, consideration is needed as to how this technology will be applied. The potential for WGS to detect asymptomatic carriers of a range of conditions begs the question, could WGS be incorporated into population screening programs such as newborn screening (NBS)? Recent international research into opinions of genetics professionals towards such use concluded that there remain significant logistical and ethical hurdles before WGS could be used in NBS (Ulmet al., 2014, *Journal of Genetic Counseling,* 24:452–463).). *Aim:* To identify health professionals' attitudes towards the potential use of WGS in NBS programs in Australia. *Methods:* Genetic counselors, clinical geneticists, NBS and WGS laboratory personnel, midwives and pediatricians will be invited to participate via professional organizations (N $\sim$ 34,000). Participants will complete an anonymous online quantitative questionnaire, modified from that used by Ulm et al. (2014). Survey items will measure health professionals' views on pre- and post-test counseling requirements, consent, return and interpretation of results (including incidental findings), clinical utility, legislative protection, financial constraints and turn-around-time. Statistical analysis will be conducted using SPSS. Results will include comparison to international study findings. *Significance:* The results from this study may inform policy directions, professional considerations and understanding of logistical and ethical challenges that might impact the introduction of WGS into NBS in Australia.

110. FIRST STEPS IN THE HARMONISATION OF PLASMA AND CSF AMINO ACID REFERENCE INTERVALS IN AUSTRALASIA

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Background: Six laboratories in Australasia use the same technology to measure plasma amino acids (PLAA) and CSF amino acids (CSAA) in the investigation of inborn errors of metabolism. There is considerable variation in reference intervals (RI) for PLAA and CSAA. *Aim of Study:* To determine adult PLAA and CSAA RIs using combined data from six Australasian laboratories. *Method:* Contributing laboratories submitted PLAA and CSAA levels on individuals over 16 years of age (excluding known patients and outliers) and from the ERNDIM External Quality Assurance (EQA) program. 22 amino acids were included. Inter-laboratory variation was determined for each amino acid from the EQA results. Age and gender specific distributions for each amino acid were created and analyzed. *Results:* The between laboratory coefficient of variation (CV) for 19 amino acids was between 7.2 and 13.7% and 3 amino acids had CVs >15% (16.6–21.3%). There was no significant bias from the ERNDIM group. Reference Intervals were calculated non-parametrically. 13 amino acids had statistically significant gender medians and in general, female ranges were wider than male ranges. There were 2 age related ranges within the group (16-20 years and >20 years). *Conclusions:* Agreement was acceptable for most amino acids but significant differences for some amino acids were probably due to variation in standardization and specimen handling. Harmonization will be feasible after agreed changes to standard procedures in laboratories. Expanding harmonization to include plasma pediatric ranges and CSF is recommended after development of a working group from the participating centres.

111. SMITH-LEMLI-OPITZ SYNDROME: BIOCHEMICAL AND CLINICAL CORRELATES

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Background: Smith-Lemli-Opitz Syndrome (SLOS) is a recessively inherited disorder in the DHCR7 gene that results in reduced cholesterol biosynthesis. Cholesterol has important roles in hormones, myelination and cellular signaling. Traditionally, severity in SLOS was scored by a clinical severity score documenting the malformations present in confirmed cases. We wished to re-examine the biochemical and clinical features of SLOS in the context of the emerging importance of cholesterol. *Aims:* To correlate the clinical severity to cholesterol and 7-dehydrocholesterol levels. To correlate longevity to cholesterol and 7-dehydrocholesterol levels. To document the biochemical and clinical features in confirmed cases of SLOS. *Methods:* We retrospectively examined the records of 18 patients with confirmed SLOS and documented their clinical and biochemical features. *Results:* We examined the record of 18 patients with SLOS. Our series documents mortality in patients presenting with total cholesterol levels of $\leq$0.35 mmol/L. In patients presenting with low cholesterol we report consequences of low hormones dependent on cholesterol. In addition to the limb abnormalities previously reported, we also have found clinical and biochemical evidence of branchial arch abnormalities. *Discussion/Conclusion:* We examined the consequences of reduced cholesterol presenting with symptoms of reduced mineralocorticoid and glucocorticoid deficiency. In our series, the spectrum of anomalies included branchial arch abnormalities such as thymic and parathyroid abnormalities and we suggest that screening for the consequences of these may be clinically relevant in children with SLOS. We also report a patient with a novel mutation in DHCR7, p.N407S, in a patient who presented in adulthood with intellectual impairment.

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112. A 10-YEAR-OLD GIRL HAD MPS VI (MORATEUX-LAMY SYNDROME) WITH SYMPTOMATIC CORD COMPRESSION HAD A FALSELY REASSURING NORMAL SUPINE MRI. AN ERECT SPINAL X-RAY REVEALED THORACOLUMBAR SUBLUXATION

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Purpose: To alert clinicians to a potential limitation of MRI to detect cord compression. *Methodology:* A 10-year-old girl from a non-consanguineous family was diagnosed with Morateux-Lamy syndrome (MPS VI) at the age of 13 months. No arylsulphatase B activity detected on leucocytes. She initially presented with symptoms of spinal cord compression at C1 and C2 due to atlanto-axial instability and required a cervical posterior occiput to C5 fusion. Infusions of Naglazyme (1mg/kg every week via an infusaport) was commenced as soon as federal government funding permitted from the age of 2 years and 8 months. Routine 6 monthly clinical assessments of physical examination with annual spinal imaging from diagnosis had remained stable since the cervical spine fusion. At the age of 10 years and 2 months, neurological examination showed deterioration in her gait and sustained clonus bilaterally. She was referred to her orthopedic surgeon who arranged an early MRI. *Results:* MRI demonstrated a stable spine, compared with the film 6 months previously and no significant cord compression. Her orthopedic surgeon then ordered an erect lateral spinal x-ray that showed marked subluxation at T12/LI junction. This subluxation was not visible on the MRI as in the supine position it corrected. The patient developed urinary incontinence a few days before surgery. *Conclusion:* This patient demonstrates the importance of further investigation, including erect plain radiography of the whole spine, when an MRI fails to reveal the cause of a patient's symptoms. In this case an erect spinal Xray revealed the pathogenic subluxation.

113. ADULT RECURRENCE OF CARDIOMYOPATHY DUE TO POOR COMPLIANCE IN A FEMALE DIAGNOSED IN INFANCY WITH CARNITINE TRANSPORTER DEFECT

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Carnitine transporter defect (CTD), also known as carnitine uptake defect, is an autosomal recessive disorder caused by mutations in the SLC22A5 gene encoding the plasma membrane carnitine transporter OCTN2. CTD causes carnitine depletion, but the clinical spectrum is broad, encompassing metabolic crises in infancy, childhood cardiomyopathy, fatigability in adulthood and complete absence of symptoms. We report on a 24 year old female who was diagnosed with CTD and commenced on carnitine therapy when she developed cardiomyopathy at 9 months of age. Her older brother had succumbed to cardiomyopathy at around 18 months of age and was unfortunately diagnosed too late for treatment to be instituted. Our patient's cardiomyopathy resolved within 6 weeks on carnitine treatment and did not recur in childhood despite periods of up to 3 months of minimal carnitine, including 2 weeks without therapy. She had a normal echocardiogram at the age of 24, however ceased carnitine due to a lack of a script after moving interstate and she presented with gastroenteritis 3 months later. An echocardiogram showed severe biventricular dilatation, global hypokinesis and moderately impaired function, with a left ventricular ejection fraction of 40%. One month later, significant interval improvement was noted. The left ventricle remained severely dilated, but with an improved ejection fraction of 51% (low normal systolic function). Carnitine supplementation has dramatically altered the natural history of cardiomyopathy in CTD, achieving long-term cardiac stability. Follow up echocardiography is needed to determine whether the reinstitution of therapy will result in complete resolution of our patient's cardiomyopathy.

114. THE CHALLENGES OF MANAGING AN INFANT NEWLY DIAGNOSED WITH PHENYLKETONURIA (PKU), WHOSE PARENTS ARE OF NON-ENGLISH SPEAKING BACKGROUND AND NEW TO AUSTRALIA

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Aim: Describe the challenges of management of an infant with PKU with parents from a culturally diverse background with limited understanding of English. *Case report:* Female infant diagnosed with PKU on newborn screening; day 2 phenylalanine (phe) level 276umol/L, day 9 phe level 2076umol/L (Classical PKU >1500umol/L) to non-English speaking parents. Parents arrived in Australia 18 months earlier, father had limited understanding of spoken English and mother had no understanding of English spoken or written. They are a traditional family from a culturally diverse background. Management of PKU included, titrated volumes of PKU Anamix Infant, (based on phe levels), followed by breastfeeds with solid food being introduced at 5½ months of age. She was breastfed until 10 months of age, and phe levels monitored weekly. A number of interpreters have been used extensively with this family including phone interpreters. The family have used and continue to use a computer translation program for ongoing email correspondence. *Results:* Overall, good metabolic control was achieved, however fluctuating phe levels particularly in the second year of life, reflect challenges encountered. Challenges have included communication, use of a large number of interpreters, language translating program inaccuracies, lack of nutritional information for some traditional foods, limited multi-lingual resources. *Conclusion:* She is now 3 ½ years of age, developing normally, taking PKU supplement and having the recommended dietary protein intake of 4 grams per day. Her mother has commenced English lessons.

115. SUCCESSFUL MANAGEMENT OF PREGNANCY WITH ORNITHINE TRANS CARBAMYLASE DEFICIENCY

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Background: Maternal Ornithine trans carbamylase (OTC) deficiency with hyperammonemia during pregnancy is rare. A multidisciplinary approach is essential to optimise the outcome of such a pregnancy. *Case description:* A 29 year old (G2 P1) mother was diagnosed as OTC carrier after birth of her previous child. Dietary intervention with low protein diet commenced at 12+6 weeks of gestation. [BMI: 24–28 at 38 weeks]. Serum ammonia (26–44 μmol/L at 12 weeks) rose to 71 μmol/L at 18 weeks, due to excessive protein and less carbohydrate intake. *Management:* Non-protein energy with 25% dextrose. *Diet Hx:* Protein intake 40–60 g/day, high biological value options, small meals with less protein, no snacks for most days, lack of carbohydrates, dairy, fruits and vegetables. Laboratory parameters: Ferritin low 8μg/L, Iron low 6 μmol/L. ammonia postnatally 39–99. Concurrent medications: Maxalon, Ranitidine, Ferrograd C, L-Arginine, and elevit. *Management:* (1) Dietary protein: 60g/d. 15g / meal and 5 g / snack; carbohydrates with all meals and snacks. (2) Increase dairy (2–3 serves), vegetables and

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at least 2 fruits. (3) Use calorie king to count protein, and follow sick day regime suggested by the metabolic team. (4) Continue L-arginine supplements 2.8g 3x/d, weekly check for serum ammonia, follow up. *Outcome:* Baby girl 3.4 kg delivered by cesarean at 39 +3 weeks. Mother and baby's ammonia normal post-delivery. *Conclusion:* Involvement of dieticians in the multidisciplinary team can optimise the outcome of a pregnancy complicated by maternal OTC deficiency.

116. WITHDRAWN

117. THE USE OF A LYSINE RESTRICTED DIET IN THE MANAGEMENT OF PYRIDOXINE DEPENDENT EPILEPSY

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Pyridoxine dependent epilepsy (PDE) is an autosomal recessively inherited neurometabolic disease caused by mutations in the ALDH7A1 gene encoding α-aminoadipic-semialdehyde dehydrogenase enzyme (α-AASAD) in the lysine catabolic pathway.α-AASAD enzyme deficiency leads to accumulation of α-aminoadipic semialdehyde, piperidine-6-carboxylic-acid and pipecolic acid. Devastating outcomes including significant intellectual and developmental delay have been reported in patients despite effective seizure control after pyridoxine supplementation. We describe a nine month female with classical PDE who showed significant clinical response to a combined therapeutic approach using a lysine restricted diet in conjunction with pyrodixine and folinic acid therapy. *Aim:* To promote favourable neurocognitive outcomes through dietary modifications and pharmacological management. *Methods:* At 2 weeks of age, dietary lysine restriction 70 mg/kg/d was commenced. Pyridoxine and folinic acid were supplemented at 30mg/kg/d and 4.5mg/kg/d respectively. Neurocognitive outcomes were assessed against baseline clinical observation, Griffiths Mental Development Score (GMDS) and electroencephalogram (EEG) investigations. Dietary monitoring and evaluation was directed by weekly plasma lysine levels. *Results:* Plasma lysine levels stabilized within the lower end of the reference range, mean-70 μmol/L (52-196 μmol/L). At 18 weeks antiepileptic medications were ceased and a baseline total mental age of 11 weeks with a GQ score of 75 was determined. Clinically seizures remained absent, developmental skills, and EEG results show continued improvements from baseline. *Conclusion:* The short treatment outcome emphasizes the potential benefits of early dietary intervention as an effective adjunct in the management of PDE. Longer term clinical assessments are imperative in drawing more conclusive results.

118. TREATMENT AND EFFECTS OF LATE DIAGNOSED PKU

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Background: Phenylketonuria (PKU) is an inborn error of amino acid metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase, resulting in the accumulation of phenylalanine. Without treatment this leads to significant and irreversible neurological deficit. New Zealand has a free National Newborn Metabolic Screening Programme, screening for 28 disorders. Babies are screened between 48–72 hours of life. Parental consent required as the screening is voluntary. *Methods:* A 14-month-old fully breast fed toddler presented with developmental delay, seizures, low vitamin B12 and iron levels. A urine amino acid screen, revealed a phenylalanine peak. A diagnosis of PKU was confirmed with a plasma phenylalanine level of 1238μmol/L. Dietary treatment for PKU was commenced. Metabolic formula was given via naso-gastric tube. It was parental choice not to have newborn screening. At diagnosis weight was >99.6th centile, length 91st centile and head circumference 9th centile. Developmental age was 4–6 months. *Results:* Treatment for PKU continued for 6 months from diagnosis. Treatment was then interrupted for three months when parents removed the naso-gastric tube. Compliance improved with the insertion of a gastrostomy. Metabolic formula has never been accepted orally. Mean treated phenylalanine levels have been 275μmol/L on 7x50mg phe exchanges. At age 3 years the child is seizure-free. She is eating finger foods, walking, and has two words. Head circumference continues to track 9th centile. *Conclusion:* Late treated PKU can lead to significant improvement in neurodevelopment; however, some developmental delay remains. A specialized multi-disciplinary team approach is required.

119. ELEVATED 3,6 EPOXYDICARBOXYLIC ACIDS WERE ABSENT IN THE NEONATAL PERIOD BUT WERE MARKEDLY ELEVATED AT 12 WEEKS OF AGE IN AN INFANT WITH A PEROXISOMAL BIOGENESIS DISORDER.

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An infant girl, delivered at 37 weeks gestation via planned cesarean section, required an admission to special care nursery (SCN) due to congenital anomalies: central hypotonia, ventriculomegaly, positional talipes, liver dysfunction and malabsorption. It was also thought that the infant had experienced a stroke-like episode. A cranial ultrasound revealed asymmetric bilateral germinolytic cysts in the region of the caudothalamic groove protruding into the anterior lateral ventricles. The underlying cause for the baby's condition remained unclear while in SCN despite numerous investigations including MRI and extensive laboratory testing including non-remarkable urine metabolic screens on the third and fourth days of life. She was discharged with a diagnosis of cerebral palsy at thirteen days of age. The clinical findings were considered to be likely the result of an intrauterine bleed combined with possible obstruction from the germinolytic cysts causing asymmetric bilateral ventriculomegaly. She represented at 8 weeks of age for further investigation of liver dysfunction and failure to thrive despite adequate calories via naso-gastric feeds. Repeat urinary organic acids at 12 weeks of age showed a marked elevation of urinary 3,6-epoxy dicarboxylic acids, particularly 3,6-epoxytetradecanedioic acid. A peroxisomal biogenesis disorder was confirmed by very long chain fatty acids with elevated C26:C22 and C24:C22 ratios. *Conclusion:* Increased epoxy-3,6,dicarboxylic acids led to the diagnosis of a peroxisomal disorder in this infant. Our experience in this patient indicates that they can be absent in the neonatal period. Further research is needed to determine at what age they can be reliably detected in infants.

120. WITHDRAWN

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121. RATE OF ABNORMAL NEWBORN SCREENS SUGGESTIVE OF AMINO ACID BREAKDOWN DISORDERS DIFFERS BY REGIONAL NEONATAL INTENSIVE CARE NURSERY AND FORMULATION OF PARENTERAL NUTRITION

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Background: Parenteral nutrition (PN) may lead to elevated amino acid (AA) levels. NZ NICUs use 2 different AA solutions; Primene, designed to achieve plasma AA levels similar to cord blood and TrophAmine, which has a two-fold greater concentration of methionine, designed to achieve plasma AA levels of healthy 30-day-old breastfed term babies. *Aim:* To determine if the rate of abnormal AA levels on newborn screen differs according to NICU and AA solution. Method: National data on NICU screening tests were reviewed over a 5-year period (2010–2015). The routine protocol includes a 1st sample at 48 hours, plus repeat tests for low birth weight infants (<1500 g at 2 weeks, <1000 g at 2+4 weeks). AAs were measured by TMS. The rate of abnormal AA screens was calculated for individual NICUs and grouped according to AA solution used. *Results:* Of 15,633 NICU 1st screening samples, 609 (3.9%) had abnormal AA levels (459 with elevated methionine), and 64/3888 (1.6%) of 2nd samples and 18/1325 (1.4%) of 3rd samples were abnormal. The rate of abnormal AA levels on 1st samples ranged from 0.8-10.7% between NICUs and was 10-fold greater for NICUs that used TrophAmine as compared with Primene®. No clinically unsuspected inherited AA disorders were detected. *Conclusion:* False positive screening tests suggestive of AA disorders were especially common among NICUs that use TrophAmine. While there are sound clinical arguments behind the use of such solutions, screening programs should consider tailoring AA cut-offs to nutrition. More detailed feeding histories would be informative.

GENETIC EDUCATION, EPIDEMIOLOGY AND PUBLIC HEALTH GENETICS

122. POPULATION CYSTIC FIBROSIS CARRIER SCREENING: HEALTH PROFESSIONALS' ATTITUDES, KNOWLEDGE AND PRACTICE PATTERNS

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Cystic fibrosis (CF) is the most prevalent life-shortening, recessive condition in Australia. Most children born with CF have no family history. Population CF carrier screening can identify carriers, in the absence of a family history. Despite recommendations, CF carrier screening is not offered routinely in pregnancy and prepregnancy care. There has been limited research into health professionals' (HPs) attitudes, knowledge and practice patterns in regards to offering this test. This study explored the attitudes to, and knowledge of population CF carrier screening in HPs, identifying barriers and facilitators to offering screening. Differences in attitudes and knowledge between HPs who frequently offer population CF carrier screening, and those who do not, were investigated. Five key informant interviews informed the development of an online survey, distributed to Victorian HPs involved in prenatal care. Forty-five HPs completed the survey. Data were analyzed using descriptive statistics. 55% (24/44) of HPs completing the survey supported population CF carrier screening, with 43% (19/44) unsure whether it should be available and 2% (1/44) not supporting it. 53% (24/45) of HPs did not offer screening to all patients. Barriers to offering CF carrier screening included time constraints, lack of confidence, cost and the perception that CF carrier screening was a low priority in pregnancy-related consultations. Access to brochures, online information and genetic counseling services were facilitators to offering screening. Although HPs are not opposed to offering population CF carrier screening, they require additional information and increased awareness of available resources to overcome barriers to offering screening more frequently.

123. GENETIC HEALTH PROFESSIONALS' AWARENESS OF NSW HEALTH PRIVACY GUIDELINES ON DISCLOSURE OF GENETIC INFORMATION WITHOUT CONSENT

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Background: Genetic counseling is a family affair. Depending on the genetic information in question, concerns may arise regarding its disclosure. In NSW, two statutory instruments regulate disclosure of genetic information covering the Public sector (and aligning with Commonwealth legislation and guidelines covering the Private sector): the Information & Privacy Commission Guideline: Use & disclosure of genetic information without consent (October 2014), and the Health Legislation Amendment Act 2012. These provide for the use and disclosure of genetic information without patient consent where there is 'reasonable belief' that disclosure is necessary to lessen or prevent serious threats to life, health or safety of individuals. *Aim:* This project has been designed to assess NSW genetic health professionals' awareness and knowledge of, and attitudes towards, the above Guidelines and Legislation. It is hypothesized that these professionals lack awareness and/or knowledge in their implementation. *Methods:* 155 health professionals with genetics expertise working in NSW will be invited to participate in a novel anonymous online survey measuring relevant knowledge, attitudes and awareness. Participants will be recruited via email lists from the NSW Genetic Counselors Network (NGCN) and the Australasian Association of Clinical Geneticists (AACG), and by personal invitation from investigators. T-test and chi-squared association tests will be done in SPSS to analyze data. *Discussion:* It is anticipated that results will identify gaps in knowledge and potential challenges which will inform development of educational strategies to increase awareness and support genetic health professionals in disclosure of genetic information, when indicated or appropriate.

124. EFFICACY OF THE EDUCATION PROVIDED IN THE SYDNEY JEWISH HIGH SCHOOL GENETIC CARRIER SCREENING PROGRAM

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Background: The Ashkenazi Jewish population is at increased risk for being a genetic carrier of several autosomal recessive (AR) conditions compared to the general population. This prompted the inception of the Sydney Jewish high school genetic carrier screening programs in 1995, for Tay-Sachs disease (OMIM

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#272800). Multiplex and Next Generation/Massively Parallel Sequencing (NGS/MaPS) are being progressively introduced, allowing the genetic carrier screening program to increase from the current nine AR conditions in future years. A compulsory education session is delivered to year 11 students, followed by voluntary testing several days later. *Aims:* We aim to evaluate the retention of knowledge, and changes in attitudes and/or concerns in participants, one-year post-genetic carrier education and screening. *Method:* We recruited a sample of Jewish high school students participating in the Sydney program across four schools (n=167). An adapted, validated questionnaire was anonymously administered, before the education session, immediately after, and 12 months post-education and testing. *Results:* Despite the increased number of conditions covered by the screening program, there was increased knowledge immediately post-education, but increased concern regarding individual carrier status. *Discussion:* The information provided to students is likely to be more relevant later in life with regards to family planning. The retention of knowledge and long-term impact on student outcomes is therefore an important issue. This research will allow us to evaluate the efficacy of the program, and the impact on student outcomes of broadened testing menus enabled by NGS/MaPS.

125. EXPLORING AUSTRALIANS' UNDERSTANDING OF GENETIC CONCEPTS IN THE ERA OF PERSONAL GENOMICS

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Background: Healthy individuals can now access their genetic information about, and its implications for, health, ancestry, paternity and sporting ability. 'Personal genomic' testing has predominantly been marketed within the USA, but will become routine and accessible to everyone, including Australians. *Aim:* To explore Australians' perceptions and understanding of personal genomics. *Methods:* Seven focus groups were conducted in Melbourne and Sydney with 56 members of the public assigned into 3 age groups: 18–25, 26–49 and $\geq$50 years. Three researchers coded transcripts independently and generated themes. *Results:* Themes focused on awareness of personal genomic testing and genetic literacy. No-one recognized the term 'direct-to-consumer' testing; most were not familiar with 'personal genomic testing', but could infer the meaning of 'personal genomics'. Participants' descriptions of DNA, genetics and genomics varied according to prior experience and education. Although familiar with ideas of inheritance and genetic influences on physical characteristics, perceptions of the relative influence of genetics and environment on health, mental health, behavior, talent or personality were varied. While many felt their own understanding of genetics was limited and did not mention specific terms (eg epigenetics), they contributed meaningfully to discussions using descriptive language. *Conclusion:* These focus groups demonstrate challenges of using specific, jargon-laden terms in public discussions. These findings have also informed development of an online survey on personal genomics which is being launched nationally around DNA Day in April. Together, these research findings can contribute to more engaging services and educational resources for individuals to understand and make decisions around these tests.

126. FILLING THE VOID: A SUPPORT INITIATIVE FOR FAMILIES AFFECTED WITH A RARE CONDITION LIVING IN RURAL/REMOTE AUSTRALIA.

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Background: Living with a rare genetic condition and/or caring for someone with a rare genetic condition is associated with significant social and emotional impacts. These are even more pronounced for families in rural/ remote areas with added difficulties of geographic isolation, limited access to services and lack of appropriate community support. Genetic Alliance Australia was created in 1988 to provide a national umbrella group for information dissemination and representation of those impacted by rare genetic conditions. *Method:* Filling the Void (FTV) uses a collaborative approach between carers/ families and professionals to respond to the various needs of those living in isolation affected by rare genetic conditions. Individuals / families are referred by professionals, friends, family or self-referral and contact is made via phone, email, web or social media inquiry. The outreach program is delivered through a series of rural seminars, sibling workshops, networking events and tele-counseling groups. *Results:* FTV has been running for over 10 years. Evaluation and monitoring of the program has shown a persistent positive feedback from participants. As a response to the changing environment where information is more easily accessible, the program is looking for innovative ways to meet consumers' need. Communication with health professionals underlined the necessity to engage with early educators and allied health professionals to ensure that families' needs are met. *Conclusion:* Rural/ remote outreach support in Australia is strongly needed. Strong collaboration is necessary to keep up with its constant evolution and its expansion to professionals.

127. THE EVOLUTION OF AN ANNUAL INFORMATION MODEL FOR BRCA1/2 GENE FAULT CARRIERS AND THEIR SUPPORT PEOPLE

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Introduction: Individuals with BRCA1/2 gene faults are a unique group with specific support needs. Genetic Alliance Australia (GA), a peak umbrella organization, was approached by a consumer and a genetic counselor in 2001, seeking support for BRCA1/2 gene fault carriers. The outcome was an annual BRCA1/2 information day hosted by GA for 15 years, an alternative to traditional support group models. GA documented how this unique model evolved with patients' support needs over time. *Method:* Qualitative and quantitative data was collected and analyzed from completed evaluations over 15 years. Patients' perspectives and suggestions for improvements/topics for the day were recorded and logistical elements analyzed. *Results:* Evaluation results showed on average 73% of annual attendees were new. GA continually re-evaluated and modified the format based on feedback, catering to new and repeat attendees. Participants consistently responded positively to the diversity of information presented and appreciated opportunities to ask health professionals questions in a non-clinical setting. Participants appreciated hearing personal stories and embraced the opportunity to communicate and share their experiences with others who were at different points in their journey with BRCA1/2 gene faults. Life changing decisions and challenges were openly shared. Partnership with familial cancer genetic counselors and consumers has grown from a

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consultative group into a cohesive and integrated partnership. *Conclusion:* The BRCA1/2 Information Day provides a non-clinical, face-to-face approach focusing on mutual aid among participants. It has evolved into a unique hybrid of support group and information day models, driven by consumers' needs, demonstrating its portability.

128. MIGRATION OF THE SYDNEY ASHKENAZI JEWISH TAY-SACHS AND COMMUNITY GENETICS SCREENING PROGRAM: LESSONS FOR THE BROADER GENETICS COMMUNITY

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Background: The Sydney community genetics program has been available to the Ashkenazi Jewish (AJ) community for 25 years. It offers autosomal recessive genetic carrier testing so couples potentially at-risk of having affected children can make informed reproductive decisions. The program recently relocated to a new host institution, SEALS Genetics, at Prince of Wales Hospital, Randwick. *Aims:* To successfully transfer without interruption the Sydney AJ community genetics program between hosts. *Results:* Program organisers consulted closely with the community: although collections occurred without interruption, school reporting was temporarily changed from annual to biennial during transfer. Testing migrated to DNA-only using 2mL saliva as the preferred community sample type. Verification to meet NATA and NPAAC requirements was undertaken. Both positive and negative controls were evaluated, as well as sample types including saliva, blood, chorionic villi and amniotic fluid. Multiplex ARMS AJ and European cystic fibrosis assays were implemented. These test for 66 variants in 9 genes with significantly higher AJ carrier rates than general population. The transfer also included redesign of request forms and reports, and physically transporting all stored specimens and migrating historical results. *Discussion:* The transfer was ultimately considered a great success, with full resumption of all community testing access routes. However, two unexpected but valuable lessons emerged: (1) Migration to DNA-only testing accelerated groundwork for Massively Parallel Sequencing (MaPS), using existing assays for confirmatory testing. (2) Corporatization of pathology services can place at risk charitable donations of equipment and funds. Strengthened governance is recommended to clarify ownership and prevent appropriation.

129. 'KEEPING IT IN THE FAMILY' — CONSANGUINITY IN TASMANIA VERSUS MAINLAND AUSTRALIA

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Background: Genetic professionals who work in Tasmania frequently encounter the perception that there are higher levels of inbreeding in the Tasmanian population compared to elsewhere in Australia. The use of SNP microarrays for molecular karyotyping provides the opportunity to test this hypothesis by analysing levels of homozygosity in patients from Tasmania and comparing them to patients from mainland Australia. *Methods:* We analyzed data from SNP microarrays for all cytogenetic referrals received by VCGS Cytogenetics Laboratory between 2013 and 2015. The presence and number of Long Continuous Stretches of Homozygosity (LCSH) were analyzed for each sample and analyzed according to patient postcode. *Results:* Between 2013 and 2015, 14,793 SNP microarrays were performed at VCGS. Samples were referred from patients living in Victoria, Tasmania, Queensland and the Australian Capital Territory. LCSH greater than 5 megabases in length was detected in 1348 (9.1%) of all samples. For Tasmanian samples, the proportion with LCSH was 5.2% (70/1357) which was significantly lower than for samples from mainland Australia, where LCSH was detected in 9.5% (1278/13436) ($p<0.01$). LCSH was detected most frequently in patients from Victoria (1085/10510 referrals, 10.3%). A high level of LCSH, defined as LCSH>6.25% and corresponding to parental relatedness closer than first cousins, was detected in 9/1357 (0.66%) of Tasmanian samples compared to 164/13436 (1.2%) of referrals from mainland Australia. *Conclusions:* Contrary to the popular perception, parental consanguinity appears to be less common in the Tasmanian population than in the mainland Australian population.

130. GENOME-WIDE ASSOCIATION STUDY OF PROLIFERATIVE DIABETIC RETINOPATHY AND DIABETIC MACULAR OEDEMA

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Background: Diabetic retinopathy (DR) is a sight-threatening complication of diabetes mellitus and a leading cause of blindness worldwide. While genetic risk factors have been reported for DR, none have been reported individually for proliferative diabetic retinopathy (PDR) or diabetic macular oedema (DMO), the main complications that affect vision.

Aim: To identify novel genetic risk factors for PDR and DMO. *Method:* Caucasian Australians with type 2 diabetes mellitus were evaluated for retinopathy status. Two genome-wide association studies (GWAS) were conducted; the first to compare PDR cases ($n = 167$) with diabetic controls (n=422) and the second to compare DMO cases (n=270) with diabetic controls ($n = 435$). Genotyping of single nucleotide polymorphisms (SNPs) was carried out on the OmniExpress SNP array (Illumina). Published DR loci were assessed in both data sets. *Results:* The top-ranked SNP in the PDR GWAS was rs918520 ($p = 1.94E^{-}06$, OR = 0.30 95% CI [0.18, 0.49]) on chromosome 5 near the LOC285626 gene. In the DMO GWAS, the top ranked SNP was rs1990145 ($p = 4.10E^{-}06$, OR = 2.02 95% CI [1.50, 2.72]) on chromosome 2 near the MRPL19 gene. Two previously reported SNPs showed a trend towards association; rs12267418 ($p = .0075$) in the DMO cohort and rs16999051 ($p = .0067$) in the PDR cohort. These SNPs are associated with the MALRD1 and PCSK2 genes respectively. *Discussion:* Although no SNPs of genome-wide significance (p <5E-08) were found in this study, findings from a previously published GWAS

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for sight-threatening DR were supported. Further research with larger sample sizes are needed to determine the importance of these SNPs.

131. GLYCOSYLATION OF IMMUNOGLOBULIN G AS A LINK BETWEEN CHRONOLOGICAL AND BIOLOGICAL AGE

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Background: Altered immunoglobulin G (IgG) glycosylation, an important post-translational modification, is associated with ageing, causing downstream effects on inflammatory pathways. Recent research suggests that IgG glycosylation can be used as a predictive biomarker for chronological age in European populations, but to date there are no comparable data from China or Australia. *Aim:* To enhance our understanding of the role of glycosylation in the ageing process, the heterogeneity of IgG N-glycans and their utility as biomarkers of chronological age in two cohorts from Australia and China were investigated. *Methods:* Participants were recruited from community-based cohorts in Beijing, China (Suboptimal Health Study, $n = 701$, age range: 23–68) and the City of Busselton, Australia (Busselton Healthy Ageing Study, $n = 700$, age range: 46–67). Participants at both sites completed comprehensive questionnaires, a detailed clinical examination and provided fasting blood samples. Predictive models of chronological age were constructed using all-subsets and binomial regressions. *Results:* Major changes were identified in the profiles of 11 N-glycans with advancing chronological age. Different combinations of these glycans could explain 23%-45% of the variation in chronological age, and the combined glycan profiles were additionally associated with clinical traits, such as fasting plasma glucose. *Conclusion:* With the support of the Australia-China International Collaborative Project (NHMRC-APP 1112767-NFSC 81561128020), a full-scale validation study will be conducted into the effect of chronological age on IgG N-glycan heterogeneity. This will be conducted in Australia and China to reveal whether IgG N-glycans can serve as generic biomarkers of ageing in the general populations.

132. THE PREVALENCE AND PROFILE OF CONGENITAL HEART DEFECTS IN DOWN SYNDROME: A 30-YEAR STUDY

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Background: Congenital heart defects (CDs) are frequently diagnosed in people with Down syndrome (DS), often with a poor prognosis if untreated. *Research question*: To investigate the prevalence and profile of CHDs in people with DS born in Western Australia, via a whole population approach utilizing four linked population-based datasets. Methods: DS cases born 1980–2009 were sourced from the WA Disability Services Commission database, the primary registration point for people with intellectual disability in Western Australia, complemented by three additional State databases containing codes for DS — Hospitalizations, Death Records, and the WA Register for Developmental Anomalies. *Results*: One or more CHDs were diagnosed in 379/852 (44.5%) of people with DS for whom birth defects were recorded. Although 30 different CHDs were diagnosed, >80% of defects were classified into four major types: ventricular septal defects (22.8%), atrial septal defects (21.5%), atrioventricular septal defects (20.0%), and patent ductus arteriosus (17.0%). *Discussion*: CHDs have variously been estimated to occur in 8–12/1,000 to 50+/1,000 of the general population, depending on method of diagnosis, age at investigation, and symptom severity. The present study confirmed a significantly elevated prevalence of CHD in people with DS, and demonstrated a dissimilar overall profile of CHDs compared to the general population. Ongoing investigations support the hypothesis that the major increase in life expectancy among people with DS during the last 50 years can largely be ascribed to successful early CHD correction. However, the reason(s) for the high rates of specific types of CHDs in individuals with DS remain unresolved.

133. WITHDRAWN

134. THE EARLY ONSET SCOLIOSIS BIOBANK INITIATIVE

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Early-onset scoliosis (EOS) develops before the age of 10 years and is a heterogeneous condition with poorly understood etiologies. EOS is a rare disorder and for some children, the deformity may become life threatening.

This study aims to establish an Australian DNA/proteomic/glycomic biobank for EOS at Edith Cowan University (ECU). *Methods:* This multi-institutional, longitudinal, prospective study aims to recruit participants (EOS patients) and family members consecutively, with the number of samples increasing over time. Participant recruitment will be based according to etiological subgroups (congenital, neuromuscular, idiopathic, and syndromic), with collection of samples and data commencing from the end of 2015 through to the end of 2025. Venous blood samples will be collected in local participating children's hospitals throughout Australia. Samples will be transported, processed, and stored at -80 for DNA/RNA as buffy coat and -196 degrees Celsius for protein and glycan analyses as plasma and/or serum, under the governance of the School of Medical Sciences, Edith Cowan University. Phenotypic data of each participant will also be collected. *Significance:* Establishing a pilot bio-bank will allow further genomic, proteomic, glycomic and genetic epidemiological studies in a rare yet debilitating childhood disorder. Once established, the EOS biobank has the capacity to broaden its scope to include other rare diseases. Collaboration, both transnationally and internationally, in the field of RD biobanking, would be possible. Future studies are needed to fully elucidate the etiopathogenesis of EOS. This is especially so given consideration of its bleak prognosis, burden to society, and significantly increased morbidity/mortality rate.

135. INVESTIGATING THE USE OF GENETIC INFORMATION BY LIFE INSURERS IN AUSTRALIA

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As genetic testing in health care increases in prevalence, concerns have been raised about genetic discrimination (GD). Funded by the Australian Research Council, the Genetic Discrimination Project (2003) explored views and experiences of individuals who had undergone predictive testing, and found that a primary concern

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related to impact of genetic testing on life insurance eligibility. Otlowski et al (2007) conducted an independent audit and analysis of underwriting decisions between 1999 and 2003, using data provided by the Investment and Financial Services Association (IFSA). Data collected from member life insurance companies included the insurance applications with genetic test disclosures, provided to researchers for the purposes of an audit. GD was identified in several cases with inaccurate risk assessments by underwriters resulting in unjustified policy exclusions. Our study follows the same methodology as the previous audit, using both the original data and newer data provided by the Financial Services Council (formerly IFSA) for the period 2011 to 2015, allowing for direct comparison between data sets. Aims include: identification of volume of genetic test result disclosures; examination of cases containing test results that influenced underwriting; explore GD issues identified from a legal perspective; comparison with the previous study to monitor changes in volume of, and underwriting practices in relation to genetic test disclosures. We hypothesize an increase in genetic test disclosures, in line with the increased use of genetic testing in healthcare; however, pre-test counseling and discussion of life insurance prior to consent should result in majority of test disclosures being negative results.

136. FULFILLING THE PROMISE OF PERSONALIZED MEDICINE — PRIORITIZING OUR INVESTMENT

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Numerous first world countries are beginning to make substantial investments in next generation sequencing (NGS) and genomic medicine with a view to delivering improved health outcomes to its citizens. But with so many promising applications of genomics, potentially very large costs and many countries struggling under the weight of sovereign debt, it is crucial that we make prudent early investments that are both effective and deliver value for money to fulfil the promise of personalized medicine. We examine evidence for a framework for investment in improving population health using (NGS) and genomic medicine. We analysis data on genetic testing and its effects in terms of incidence reduction of a range of conditions, and based on this evidence, provide guidance on where the greatest benefits from genomic medicine might be initially be achieved. We conclude that the individuals who are uniquely placed to gain immediate benefit from personalized genomic medicine are those who can be identified as being at high risk of imminent, serious, preventable, penetrant, and costly disorders.

137. THE SOCIAL AND ECONOMIC IMPACTS OF CHILDHOOD SYNDROMES OF SUSPECTED GENETIC ORIGIN

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As part of a prospective study on the 'Integration of genomic sequencing into clinical care' at the Royal Children's Hospital in Melbourne, Australia, we undertook a detailed survey of the social and economic impacts of childhood syndromes of suspected monogenetic origin among the infants aged 0–2 years. In this paper, we report on the first wave of our survey on the quality of life impacts on the parents, their current labour force participation and income, impacts on their family planning behavior, the parental marital relationship and social connectedness. Preliminary analyses show that 54% of the infants experienced hospitalization in last one year and 68% parents compelled to work part-time, and 18% are not in labour force. More than half of the parents (54%) have concerns of further recurring genetic disorder among their future children and 82% are taking steps to avoid pregnancy. However, two thirds of the parents maintain healthy parental relationship.

138. WITHDRAWN

139. PROGRAM OF GENOMICS RESEARCH: IMPLEMENTING STREAMLINED ETHICAL REVIEW AND RESEARCH ADMINISTRATION

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The Sydney Children's Hospitals Network (SCHN) research strategy called for capacity and capability building in genomics research. A key initiative has been the harmonization of approaches for human ethics applications in genomics research projects. We report on implementation of a cohesive model for streamlining administration, ethical review and consent processes in genomics research. In response to growth in genomics research, the Genomics for Rare Diseases Program of Research (SCHN) was designed to provide a common pathway for genomics research. This is an overarching framework facilitating the use of phenotypic data and genomic sequencing methodologies that may be applied to different research questions. Wide consultation with interested parties within the Network informed content of the National Ethics Application Form (NEAF) and associated documents. The Program was approved by the SCHN Human Research Ethics Committee (HREC). Within this structure, principal investigators with a relevant research question may submit a Specific Project Research Plan to the Program. Research Ethics and Governance approval of Specific Projects under the Program has been simplified under local programs of research policy, thereby enabling genomics research. National Mutual Acceptance, a system of single ethical and scientific review of multicentre research in Australia was recently extended beyond clinical trials, to include all human research. Opportunities therefore exist to broaden the scope for the Genomics for Rare Disorders Program of Research beyond SCHN. Implementation at other sites is in progress. Such an approach is essential in facilitating multi-centre genomics research collaboration for rare diseases affecting both pediatric and adult populations.

140. WITHDRAWN

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