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Oral Presentations

Australasian Society of Cytogeneticists and Molecular Genetics Society of Australasia Workshop
THE PRAGMATICS OF NAVIGATING THE UCSC BROWSER: A WORKSHOP

Robert Kuhn

UCSC Genome Browser Center for Biomolecular Science & Engineering, Baskin School of Engineering, Santa Cruz, CA, USA

The UCSC Genome Browser workshop will provide an interactive forum for hands-on instruction in the use of the Browser and associated tools. Participants will load their own Custom Tracks onto the Browser, make and retrieve their own saved sessions, and explore the UCSC Genes track, which is a gateway to a large number of external databases. They will also learn how to use the Table Browser to pull customized data from multiple, linked tables. Participants should bring their own fully charged laptops and come prepared to ask questions.

Australian Society for Inborn Errors of Metabolism Oral Presentations
ASIEM Oral 1
INBORN ERRORS OF METABOLISM IN PACIFIC AND MAORI CHILDREN

Callum Wilson[1], Emma Glamuzina[1], Don Love[1], Detlef Knoll[1], Rhonda Akroyd[1], Dianne Webster[1]

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Particularly high incidences of specific metabolic diseases are well described in certain ethnic groups. This can be due to high rates of consanguinity but usually reflects the founder effect whereby a common ancestor of a genetically isolated population is a carrier of a recessive disease. The Pacific region is made up of a number of distinct ethnic groups and thus one would expect certain genetic diseases to be more common. New Zealand (NZ) has the largest population of Pacific peoples in the world as well as being home to a large, genetically distinct, indigenous Maori population. Since the establishment of a national clinical metabolic service in 2001 a number of inborn errors of metabolism have been identified that occur at a high incidence in particular Pacific or Maori populations. These include non-ketotic hyperglycinemia, very long chain acyl CoA dehydrogenase deficiency and X linked adrenoleukodystrophy in NZ Maori, biotin resistant holocarboxylase synthetase deficiency (HCS) in Samoan children, and carnitine palmitoyl transferase type 1 deficiency and citrullinaemia type I in Niuean individuals. There are also a number of very rare and in some instances new diseases that have been identified. Knowledge of these diseases and their ethnic distribution can help with newborn screening and also aid the clinician when assessing the patient with suspected metabolic disease. As well as being of diagnostic benefit, specific therapies such as high-dose biotin and referral for liver transplantation in HCS could be implemented.

ASIEM Oral 2
RCPA GENETIC TESTING SURVEY FOR BIOCHEMICAL GENETICS

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Background: In 2012, the Royal College of Pathologists of Australasia conducted a survey of Australian genetics laboratories, commissioned by the Federal Government Department of Health and Ageing. The survey was a repeat of one conducted in 2006 but this time included data on Biochemical Genetics tests. *Methods:* 100% of invited laboratories, identified through NATA accreditation scope of practice, participated and the survey covered the 2011 calendar year. Data were collected by electronic means and then collated for analysis. To allow meaningful comparisons between jurisdictions, multi analyte panels (e.g., leucocyte enzymes) were counted only once. *Results:* There were 6 major biochemical genetics labs in 5 states. 111 separate biochemical genetics test targets were returned. Only 4 were offered in all laboratories and 84 were available in only one centre. A total of 77407 tests were performed in 2011. Total testing rate per head of population varied over 6 fold across the States. For the 3 most common assays, testing rates per head still varied markedly. Significant transfer of tests between States took place with over 5000 tests referred, most paid for by the referring lab. Funding was predominantly from the States but with significant variation between States in the proportion of costs borne by patients, ranging from 0 to 85%.

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ASIEM Oral 3
URINE TANDEM MASS SPECTROMETRY SCREEN FOR INBORN ERRORS OF METABOLISM: THE CHRISTCHURCH EXPERIENCE

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Since August 2012 we have been reporting aminoacids analysed by direct injection of butylated samples and internal standards into a tandem mass spectrometer (MSMS). Over an 18-month period prior to this, 520 patient urines were assayed by qualitative thin layer chromatography (TLC) and the new MSMS method. By both methods, 484 showed no abnormality, 8 generalised aminoaciduria, and 9 showed an abnormality (s-sulphocystine in Molybdenum cofactor deficiency(1); homocystine in Vitamin B12 deficiency(1); cystine and dibasic aminoacids in Cystinuria(3), probable Heterozygote Cystinuria(1) and arginine infusion(1); tyrosine in liver dysfunction(1); and homocitrulline(1). The TLC method showed aminoacid elevations in 11, whereas these samples were normal by the MSMS method (generalised increases(7), glycine(3) and slight increased branched chain aminoacids(1). Another showed normal TLC but a small arginine increase on MSMS using the cut-off level determined by Pitt et al. 17 out of 18 Quality assurance samples and 3 out of 3 known patients with an IEM in aminoacid or creatine pathways were elevated by both methods. In 1 (ASIEM 2004-08) the tyrosine was increased by TLC and quantitative HPLC but within the MSMS cut-off value used. Our experience developing the aminoacids and the on-going development for the remainder of the positive ion and negative ion metabolites will be discussed.

ASIEM Oral 4
DIETARY MANAGEMENT IN LONG CHAIN FATTY ACID OXIDATION DEFECTS: A CHANGE IN CLINICAL PRACTICE AT RCH

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Long-chain fatty acid oxidation disorders (FAOD) vary in presentation, severity and outcome. Treatment recommendations depend on individual disease severity. At RCH, Melbourne, our standard practice has been to prescribe a very low-fat diet with MCT supplementation to infants diagnosed with a long-chain FAOD, indefinitely. We questioned whether these dietary restrictions were necessary long term for all children. To this end, we conducted a literature search using Medline 1996–February 2013 (MeSH terms: acid, defects, fatty, fatty oxidation, defects, oxidation) to identify articles providing clinical audits and evidence-based guidelines. We collected retrospective clinical and dietetic data from all health records of all children diagnosed with a long-chain FAOD at our centre (February 2002–April 2011). Patients with episodes of metabolic decompensation and/or muscle pain with high CK (with or without rhabdomyolysis) were defined as symptomatic.

Four papers (reporting 191 patients from 20 centres) were selected for review. There were 16 patients with VLCAD deficiency (current age range: 11 months–10 years): 11 have remained asymptomatic; 2 had metabolic decompensation in the neonatal period; 4 had episodes of muscle pain and high plasma CK. There was one patient with CPT I deficiency, current age: 3.5 years, who is asymptomatic and two patients with CPT II deficiency (current age range: 6–8.5 years); one symptomatic, the other asymptomatic. Asymptomatic children with long-chain FAODs are given the option of following the 'healthy recommended' diet providing 30% total energy from fat. MCT supplementation is used at times of increased energy demand only (e.g., around sports activities). This practice requires further validation.

ASIEM Oral 5
OUTCOMES OF MATERNAL PHENYLKETONURIA PREGNANCIES MANAGED IN NEW ZEALAND

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Introduction: The possible teratogenic effects of maternal phenylalanine on the fetus are well described including facial dysmorphism, microcephaly, developmental delay, intrauterine growth restriction, and congenital heart disease. To prevent these complications, women with phenylketonuria (PKU) are encouraged to have planned pregnancies and aim for pre- and post-conception phenylalanine levels of between 100–300 μmol/L. *Objective:* To review pregnancies of women with PKU, managed by the National Metabolic Service for New Zealand. *Method:* Clinical and laboratory data was collected retrospectively for pregnancies occurring between 1997 and 2013. *Results:* A total of 46 pregnancies resulted in 30 live births, 6 miscarriages and 10 terminations, of which 5 were medically advised. Eight pregnancies occurred in women on preconception diet, 12 women were on an adult PKU diet and 26 women were off diet preconception. Four pregnancies resulted in fetal anomalies, one with acrania requiring termination of pregnancy (TOP) and one with a meningocoele. The same mother had a subsequent medical TOP for megacystis secondary to posterior urethral valves. One twin pregnancy resulted in one healthy live birth and one stillborn complicated by multiple fetal abnormalities. Three of these four cases were associated with poor maternal diet adherence. *Conclusion:* Diet management in maternal PKU is challenging, particularly when woman have been off diet prior to conception. Complications of poor diet control are preventable by maintaining tight phenylalanine restriction throughout pregnancy. There may be an association between the relatively high proportion of miscarriages and fetal anomalies and low numbers of women on pre-conception diet.

ASIEM Oral 6
THE INTRODUCTION AND EVALUATION OF AN EVIDENCE BASED PROTOCOL AND EDUCATION PACKAGE FOR THE IMPLEMENTATION AND MANAGEMENT OF BH4 THERAPY FOR PATIENTS

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Tetrahydrobiopterin (BH4) is a relatively new treatment option for patients with Phenylketonuria (PKU). An application for BH4 has been submitted for approval to the Pharmaceutical Benefits Scheme in Australia. If BH4 is approved, implications for management and treatment of patients will be significant. International authors have concluded that clinical protocols are required for managing dietary change while maintaining control of blood phenylalanine, ensuring adequate nutrition, preventing deficiencies and excess weight gain.

Due to the relatively small size but wide geographical spread of the Australasian population, the development of an evidence-based, collaboratively agreed protocol in Australasia is essential and would benefit the multidisciplinary team in all centers.

Funding was obtained by the ASIEM Dietitians BH4 Working Party to work alongside the ASIEM BH4 Working Party to devise a standardised protocol and education package for the implementation and management of BH4 therapy for patients with PKU in

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Australasia. All centers will be invited to participate and contribute to the outcome of this project.

A prospective, Delphi survey will be given to all metabolic team members involved in patient care for people with PKU across Australasian clinics. The survey will consist of targeted questions from the current available evidence on BH4 therapy to gain consensus for proposed patient management in Australasia. A prospective telephone-based survey will be used with patients and carers across all age groups to assist in identifying areas of patient/carer concern and education requirements related to the introduction of BH4 therapy. Results will be used in the development of the protocol.

ASIEM Oral 7
DOES HYPERGLYCAEMIA CONTRIBUTE TO CIRRHOSIS IN GLYCOGEN STORAGE DISEASE DUE TO PHKG2 DEFICIENCY?

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Background: PHKG2 is a rare cause of glycogen storage disease type IX. There is a high incidence of liver cirrhosis in reported cases but etiology is unknown. *Case report:* We report a pair of siblings with homozygous mutations in the PHK2 gene. The oldest was referred for assessment by our team after he was identified as having short stature, liver dysfunction and hepatomegaly with liver biopsy demonstrating portal bridging fibrosis, nodule formation and prominent cytoplasmic glycogen. Subsequent fasting studies showed hypoglycaemia (2.1mmol/L) and ketosis (5.6 mmol/L) and hyperlipidaemia. The younger sibling was seen at 30 months with hepatomegaly and liver dysfunction ALT-938(10-50U/L), AST 1434(10-50U/L). He had commenced regular Pediasure for short stature but the LFTs deteriorated ALT1511, AST2369. Substituting the Pediasure with uncooked cornstarch led to improvement in LFTs Äì AST 736, ALT 604 with concomitant improvement in lipid profile. He too had a low fasting lactate 0.9 mmols/L and glucose 2.0 mmols/L with ketosis 3.33mmol/L with post-prandial lactate elevation after a modified glucose tolerance test of 5.5 mmols/L. Management with a low glycemic index based diet and cornstarch led to stable biochemistry and improved growth. *Conclusion:* Liver function in some forms of GSD could deteriorate with excessive simple sugar.

ASIEM Oral 8
IMMUNOMODULATION AND ENZYME REPLACEMENT THERAPY FOR INFANTILE ONSET POMPE DISEASE: AUSTRALIA'S FIRST CASE

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Glycogen storage disorder type II, Pompe disease is caused by deficiency of acid alpha-glucosidase (GAA), which is required for the degradation of lysosomal glycogen. Enzyme replacement therapy (ERT) for infantile Pompe disease has improved survival; however, there is marked variability in clinical outcomes as a result of many factors, including CRIM (cross-reactive immunologic material) status. CRIM negative status is associated with a poor response to ERT due to the formation of antibodies to rhGAA. We report the induction of immune modulation in a CRIM-negative patient with high-titre antibodies developed within 12 months of starting ERT.

Our patient with CRIM negative Pompe disease started ERT at age 4 months. Initially there was a noticeable improvement in his muscle strength. Antibody levels rose steadily; however, given the ongoing clinical improvement it was decided not to immunomodulate. At 1 year he suffered with pneumonia, which was complicated by an episode of aspiration. Continuous BiPAP and naso-jejunal tube feeds were then required. The antibody levels reached a maximum of 819,200, associated with infusion-related adverse reactions of escalating severity. In view of the rising antibody levels and the poor clinical response he commenced immunomodulation therapy with rituximab, followed 2 months later by bortezomib, methotrexate and high dose intravenous immunoglobulin. At 19 months the patient's antibody levels have fallen, the infusions are better tolerated and his clinical condition has stabilised.

Immunomodulation should be considered in CRIM negative infantile onset Pompe disease in patients with rising antibody titres and declining clinical response to ERT.

ASIEM Oral 9
HAEMATOPOIETIC STEM CELL TRANSPLANT FOR THE TREATMENT OF CEREBRAL X-LINKED ADRENOLEUKODYSTROPHY IN NEW ZEALAND

Emma Glamuzina, David Perry, Lochie Teague, Callum Wilson
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X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by mutations in the ABCD1 gene which encodes the peroxisomal membrane adenosine triphosphate binding cassette transporter protein (ALD-P). Accumulation of very long chain fatty acids (VLCFA) results in variable CNS demyelination and adrenal insufficiency. The rapidly progressive cerebral form of X-ALD affects some males classically between 3 and 10 years of age and rarely adults. Treatment is replacement of brain microglial cells with early Haematopoetic Stem Cell Transplant (HSCT). The mechanism by which this corrects the metabolic defect and stops the neuroinflammatory demyelinating process is not fully understood; however. the key to successful outcome is early diagnosis and treatment.

The National Metabolic Service for New Zealand has followed and treated 18 males with X-ALD. In 2013, 14 are alive, 16 have Addison's disease, 4 have AMN. Three are under the age of 10 and being monitored with 6-monthly MR brain imaging. Five have undergone HSCT; four childhood and one adult onset cerebral disease. Two of the five were being monitored at the time. One was too young, one too old and one presented clinically. Two of five died and four had progression of disease before and after HSCT.

X-ALD is a relatively common IEM in New Zealand. The presentation of the cerebral form of this condition has been 'classical' in only one of the three children who underwent HSCT. Despite regular monitoring, extensive education and cascade testing the decision to treat with HSCT can be difficult and the outcomes variable.

ASIEM Oral 10
EARLY LIFE EVENTS AND LATER ADULT DISEASE: A LONG SHADOW CAST

Wayne Cutfield
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Traditionally it was believed that common adult diseases such as type 2 diabetes and obesity were caused by genetic risk factors and poor lifestyle. However, in recent years, early life events have been identified as a third risk category for adult disease. In the mid-1980s Barker and colleagues made a sequence of landmark observations linking reduced birth size and increased risk of common diseases in adult life; for example, diabetes, metabolic syndrome hypertension, heart disease and stroke. He subsequently proposed that the origins of adult diseases begin in utero and were caused by suboptimal fetal nutrition. Other epidemiological studies have subsequently confirmed these findings.

Our group and others have identified in children common clinical groups that appear to have developmental programming of adiposity and metabolism. Collectively these studies indicate that as there is

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deviation away from an optimal fetal environment the risks of type 2 diabetes and metabolic syndrome increase. For example, infants born too small (3% population), too large (5%), too early (5%), too late (2–3%) or first born (50–60%) display risk factors for type 2 diabetes and the metabolic syndrome. These periods of programming sensitivity for offspring extend from before conception to early infant life.

Despite detailed characterization the triggers and mechanisms for metabolic programming in each of these groups remains to be elucidated. Epigenetic changes in imprinted and other metabolic and growth genes have been proposed as the mechanism for programming based largely upon animal models of fetal malnutrition. Limited available data in humans will be discussed.

ASIEM Oral 11
SEVERE FETAL ISCHAEMIC BRAIN INJURY CAUSED BY HOMOZYGOUS PROTEIN C DEFICIENCY

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Homozygous protein C deficiency classically presents in newborns with purpura fulminans, ophthalmic complications and thrombotic stroke. We present a case of a consanguineous couple who underwent termination of pregnancy at 35 weeks gestation for severe brain abnormality in the fetus detected on 34-week ultrasound growth scan. Fetal magnetic resonance imaging (MRI) at 35 weeks demonstrated bilateral ischaemic brain injury, with resultant severe porencephaly, haemorrhagic retinal detachment, and cardiomegaly, likely secondary to cardiac ischaemia. A high-resolution SNP microarray identified long continuous stretches of homozygosity (LCSH) consistent with parental consanguinity. The PROC gene encoding Protein C was located in a region of homozygosity. Parental plasma Protein C levels were low and sequencing of the PROC gene identified a heterozygous c.1042C>T substitution in both parents, and homozygosity for this pathogenic mutation in the fetus.

This case demonstrates that homozygous protein C deficiency can present antenatally with ventriculomegaly secondary to thrombosis and, therefore, this diagnosis should be considered in this setting, even in non-consanguineous couples. Diagnosis of this condition is important as it enables accurate recurrence risk counselling and has implications for the management of future pregnancies. This case also demonstrates the usefulness of homozygosity mapping by SNP microarray to guide diagnostic testing for rare recessive conditions occurring in consanguineous families.

ASIEM Oral 12
VULNERABLE LANGUAGE SKILL DEVELOPMENT IN GALACTOSAEMIA

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Not all children with galactosaemia (GAL) experience language impairments. Currently, there are no means by which infants at risk of language deficits can be identified early. Prelinguistic communication skills of infancy underpin oral language development and may be a means by which at-risk children can be identified early to facilitate the provision of timely intervention during the critically formative period of language development. We report on the prelinguistic communication skills of two 18-month-old infants with GAL (one of each gender).

Performance scores from the two infants were analysed using modified *t* tests where comparison was undertaken for each infant to a small ($n = 3$) individual control group. Additionally, direct descriptive comparison of performance was undertaken between the two infants with GAL using a criterion level of $> \pm 1.5$ test *SD* difference in performance score as indicative of a clinically significant difference in performance between the two infants.

Results indicate that the male infant with GAL had significantly poorer prelinguistic skills than his matched peers on word production, the Social and Speech composite scores and the overall Communication and Symbolic Behavior Score. There was a significant difference in performance by the female infant with GAL, but unlike the male infant, she outperformed her matched peers on the Social composite score. The male infant with GAL was performing developmentally at a level clinically significantly below the female infant on 10 of the 11 performance measures (predominantly 3-4 SD below her performance). The findings are discussed in terms of earlier identification of at-risk children.

ASIEM Oral 13
GALACTOSAEMIA UPDATE: A MULTI-SYSTEM DISEASE

David Coman

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Classical galactosaemia (GAL) is caused by deficiency of Galactose-1-phosphate uridyltransferase (GALT). Despite being a single gene defect, clinicians and researchers alike have identified multiple points of clinical, biochemical, epigenetic and radiological abnormalities. Despite neonatal dietary intervention the neuro-cognitive outcomes remain disappointing. Deficits in expressive language, syntax, phonology and prelingual skills have all been documented. Other long-term complications include: tremor, hypomyelination, osteoporosis, and hypergonadotrophic hypogonadism in females.

Epigenetic consequences have been described, with dysregulation in MAPK signalling, regulating the actin cytoskeleton, focal adhesion and ubiquitin mediated proteolysis. The postulated endpoint being one of upregulated unfolded protein response (UPR) via apoptosis.

Secondary perturbations in the post-translational modification (PTM) process of glycosylation are well established in GAL, especially that of aberrant galactosylation of glycoproteins and glycolipids. This may help explain the white matter hypomyelination that is observed in GAL. Aberrant PTM in GAL may also provide a mechanistic cause for the increased flux through the UPR leading to cell death, but also provides a more sensitive means to monitor biochemical indices of GAL in the clinic, especially the glycan structures of IgG. MRI Diffusion Tractography and functional MRI studies are underway to further define potential maladaptive neural-connective circuitry and function.

GAL shares clinical similarities to CDG-1a in which hypergonadotrophic hypogonadism in females is commonplace. A minority of female GAL patients have sufficient residual ovarian function to attain and maintain pubertal development. This is a major health impact of the disease which requires further active research and understanding.

ASIEM Oral 14
NUTRITIONAL INTERVENTIONS IN INBORN ERRORS OF METABOLISM

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Bickel and his colleagues discovered that the treatment of a child with PKU was beneficial, but suggested that the diet should be started earlier for an optimal outcome. Soon thereafter, when a

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newborn screening test was in place, and treatment of babies was begun very early, it was very clear that dietary treatment for PKU was enormously beneficial. These observations set the stage for widespread diagnosis and treatment of PKU, and the beginning of very successful programs in newborn screening. Few controlled, evidence-based studies were performed to study these dramatic benefits. Studies of patients undergoing treatment and the early identification of the serious damage done to fetuses of PKU mothers, off treatment, have made it clear that treatment must be lifelong. Many conferences, including two NIH conferences that were held 10 years apart, while reviewing the state of PKU therapy, have shown that we lack highly specific recommendations for treatment. However, we are thrilled to see so many very productive adult persons with PKU treated since birth. Psychological and neurodevelopmental problems that have emerged in some of the treated patients must be addressed. The treatment remains largely dietary manipulations, with the inclusion of low-protein, low-phenylalanine medical foods. Pharmacotherapy currently involves only one approved drug, a derivative of the national PAH cofactor. We will discuss some of the current material about the desirable, optimal blood levels of phenylalanine to maintain. Beginning in 2010, trans-National Institutes of Health Initiative within the United States has worked to identify gaps in knowledge regarding the safety and utility of nutritional interventions in the management of inborn errors of metabolism, and which need to be filled with evidence-based research. Some of these important needs identified by this group and the suggestions as to how to address these issues will be presented.

ASIEM Oral 15
SCREENING CRITERIA: THE NEED TO DEAL WITH NEW DEVELOPMENTS AND ETHICAL ISSUES IN NEWBORN METABOLIC SCREENING

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Newborn metabolic screening is the most widespread application of screening technology and provides the most comprehensive application of genetics in health services, where the Guthrie blood spot cards allow screening for metabolic diseases in close to 100% of all newborn babies. Despite over 40 years of use and significant benefits to well in excess of 100,000 children worldwide, there is remarkably little consensus in what conditions should be screened for and response to new advances in medicine relating to program expansion. In this article, the international criteria for newborn metabolic screening are considered, and we propose that these criteria are poorly developed in relation to the baby, its family and society as a whole. Additionally, the ethical issues that should inform the application of screening criteria are often not developed to a level where a consensus might easily be achieved. We also consider that when family interests are factored in to the decision-making process, they have a significant influence in determining the list of diseases in the panel, with countries or states incorporating family and societal values being the most responsive. Based on our analysis, we propose that decision criteria for metabolic screening in the newborn period should be adapted to specifically include parent and family interests, community values, patients' rights, duties of government and healthcare providers, and ethical arguments for action in the face of uncertainty.

ASIEM Oral 16
THE USE OF 3-HYDROXYBUTYRATE IN PATIENTS WITH FAT OXIDATION DISORDERS

Kaustuv Bhattacharya[1], Troy Dalkeith[1], Sue Thompson[1], Barbara Dennison[1], Walid Matar[2], Bridget Wilcken[1], Carolyn Ellaway[1]

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Introduction: Severe fat-oxidation disorders are associated with catastrophic illnesses including encephalopathy, liver dysfunction, rhabdomyolysis, and cardiac dysfunction. The etiology of these complications includes failure to generate ketones as an end-organ energy source. *Case Series:* We present seven patients who were treated with supplemental D-L-3-hydroxybutyrate (300 Äì 900mg/kg/day). Five of these were in ICU when therapy was commenced. Four with multiple acyl-CoA-dehydrogenase deficiency (MADD) were commenced at 7 days, 3 months, and two at 5 months for: hyperammonaemic encephalopathy, after cardiac arrest, cardiomyopathy with heart failure and profound skeletal myopathy respectively. All survived initial therapy but the youngest two died at 9 months and 13 months respectively, having had recurrent acute life-threatening episodes. The remaining two patients are well, aged 10 and 6 years. One patient with HMG CoA-Lyase deficiency was commenced electively on treatment aged 3 months; the other presented with acute encephalopathy, liver dysfunction and hyperammonaemia, aged 16 years. Despite subsequent herniation of the cerebellar tonsils into the foramen magnum, he survived with intact neurology apart from cortical blindness, currently aged 18 years. One patient with carnitine-acylcarnitine translocase deficiency presented with neonatal hypoglycaemic hyperammonaemic encephalopathy with seizures and cardiac dysfunction (fractional shortening 13%.) Ninty-six hours of enteral ketones in conjunction with intravenous dextrose led to complete resolution of the cardiac findings. She has normal development at age 3 years with an improved brain MRI. *Conclusion:* The therapeutic use of ketones in hypo-ketotic disorders may resolve severe clinical defects in the acute phase sometimes before definitive dietary therapy can be achieved.

Australasian Society of Cytogeneticists Oral Presentations
ASoC Oral 1
6p SUBTELOMERE DELETION SYNDROME

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The 6p(6p24) subtelomere deletion syndrome is a rare but clinically recognisable syndrome characterized by hypertelorism, down sloping palpebral fissures, anterior eye segment anomalies, hearing loss, congenital cardiac defects, Dandy-Walker malformation, hypotonia and mild to moderate developmental delay. There are approximately 40 cases described in the literature. Here we present detailed clinical and chromosomal analysis data on 3 patients with subtelomeric 6p deletions. These patients shared the key features of this syndrome including the characteristic facial gestalt, congenital cardiac defect, hearing loss, hypotonia and developmental delay. In addition, all three patients had a characteristic verbal dyspraxia, a developmental phenotype which is therefore associated with this microdeletion. Recognition of this should alert clinicians to the possibility of this microdeletion.

ASoC Oral 2
PARACENTRIC INVERSIONS IN THE INFERTILE POPULATION – COINCIDENTAL FINDING OR CLINICALLY SIGNIFICANT?

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Inversion frequency as reported in Gardner, Sutherland and Schaffer (2012), excluding variants is 0.12–0.7% for pericentric and 0.1–0.5% for paracentric inversions. Small paracentric inversions probably go undetected. Inversions, if large enough, will result in a pairing loop at meiosis and with an uneven number of crossover events within the loop, will produce unbalanced gametes. In pericentric inversions the imbalance is for the region outside the inversion. Paracentric inversions differ in that they will produce either dicentric or acentric chromosomes and as a consequence are generally regarded as not increasing the risk of abnormal livebirth. Reviewing 2 years of inversions found in patients presenting for the investigation of infertility, inversions constitute 18% of our total abnormalities. Of all inversions, 57% were paracentric and 43% pericentric. There was no difference in the sex of the inversion carriers, that is, equal numbers of males and females. The size of the paracentric inversions may be an indicator as to the significance of their detection in infertility patients.

ASoC Oral 3
PREDICTING SEGREGATION MODE — MEIOTIC SEGREGATION ANALYSIS FROM 139 AUTOSOMAL RECIPROCAL TRANSLOCATIONS

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Pre-implantation Genetic Diagnosis (PGD) provides the opportunity to analyse the segregation modes of translocations in early embryo development. This study investigates the meiotic segregation of autosomal reciprocal translocations resulting in day 3 embryos and compares the observed segregation modes with those determined by the Jalbert (1980) postnatal predictive algorithm for imbalanced translocation segregations. A retrospective analysis was performed on 1650 day 3 embryos of 139 autosomal reciprocal translocations from 145 Monash IVF couples who had undergone PGD between 2002 and 2013. This analysis showed that 22.2% of embryos were normal or balanced (alternate segregation) and 77.8% were unbalanced for the translocation chromosomes. Of the unbalanced embryos, 20.0% showed adjacent-1 segregation, 9.9% showed adjacent-2 segregation, 17.8% showed 3:1 segregation, 1.9% showed 4:0 segregation and 28.2% showed an unknown mode of segregation. The above embryo data showed similar proportions of segregation modes compared to the predictive model. There was a similar proportion of adjacent-1 and 3:1 embryos and a lower proportion of adjacent-2 embryos. Using the Jalbert algorithm, 36.9% (609/1650) of all the embryos tested showed a segregation mode that was predicted. This figure increased to 47.4% (609/1284) when only unbalanced embryos were examined. This data represents the largest analysis of meiotic segregation in day 3 embryos. The concordance with the postnatal predictive model was weak, indicating that there is a need for a predictive algorithm specific for preimplantation embryos.

ASoC Oral 4
FURTHER INVESTIGATION BY KARYOTYPE AND FISH ANALYSIS UNCOVERS STRUCTURAL REARRANGEMENTS IN ARRAY CGH CASES

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Chromosomal microarray analysis (CMA) is currently recommended as a first tier test in cases referred for developmental delay, intellectual disability, autism spectrum disorders and multiple congenital abnormalities. However, in some cases GTG banded and/or FISH analysis can be useful as a secondary test to establish the true complexity of the imbalance detected. Two male neonates, one referred for multiple congenital abnormalities and the other for a possible syndrome (no yet diagnosed), were referred for CMA. Each showed an approximately 20Mb duplication one involving chromosome 2 and the other chromosome 12. Further investigation using GTG banded karyotype and FISH analysis showed the presence of a rearrangement involving an acrocentric chromosome in both cases. These cases highlight the need for further testing to aid interpretation through the visualisation of the chromosome abnormalities in situ. Further studies allowed for accurate recurrence risk assessment and genetic counselling for these families.

ASoC Oral 5
PGD FOR SINGLE GENE DISORDERS AT CANTERBURY HEALTH LABS: REVIEW OF DATA FROM PAST CASES, AND DISCUSSION OF FUTURE CHANGES IN METHODOLOGY

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Canterbury Health Labs (CHL) has been working with New Zealand fertility clinics to perform preimplantation genetic diagnosis (PGD) for single-gene disorders since 2006, and to date has completed over 40 clinical analyses. Protocols have been developed for 22 genetic disorders, primarily using panels of microsatellite markers in linkage with the disease gene, combined with direct mutation detection when possible. Cystic fibrosis, Huntington disease, and haemophilia A have been the most frequently requested disorders for PGD, together making up half of the cases analysed. Suitable embryos for transfer have been identified in all except one case, and the pregnancy rate is currently 30% per cycle. Initially just several cases were performed each year, but numbers have increased to 15 cases in the last year. While the methodology based on linkage analysis and single cell PCR is a successful platform, CHL is working towards a significant shift in its approach to PGD in the next year to keep pace with changing practices at fertility clinics, technological advances in molecular techniques, and raised expectations of the PGD service. It is expected that the new approach will allow direct detection of pathogenic mutations during the analysis, and the inclusion of microarray CGH to identify aneuploid embryos, and those with chromosomal abnormalities such as translocations. These changes are likely to reduce development time for each PGD case, improve the analytical workflow, and lead to better pregnancy rates per PGD cycle.

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ASoC Oral 6
NON-INVASIVE PRENATAL TESTING FOR CHROMOSOME ANEUPLOIDY: AN AUSTRALIAN COHORT OF 150 PATIENTS

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Non-Invasive Prenatal Testing (NIPT) for fetal aneuploidy is now a revolutionary new option for pregnant women seeking information about the chromosomal health of their baby without the risk of miscarriage. NIPT sources cell-free fetal DNA from a maternal blood sample and uses massively parallel genomic sequencing to quantify millions of DNA fragments. Trisomies 13, 18, 21 and sex chromosome aneuploidy may be detected as early as the 10th week of pregnancy with results available approximately 1 week after maternal sampling. The sensitivity is over 98% with false-positive rates of less than 0.5%. NIPT is currently only available in the private sector and costs approximately AU$1250 (service provider dependant). Currently, more than 120 patients have elected to undertake NIPT through the Fetal Medicine Unit at Royal Prince Alfred Hospital (RPAH). We will illustrate our experience of NIPT in this cohort, including indications for the test and outcome.

ASoC Oral 7
PRENATAL DIAGNOSIS USING COMBINED QF-PCR AND ARRAY CGH ANALYSIS AS A FIRST LINE TEST: RESULTS FROM OVER 1000 CONSECUTIVE CASES

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Objectives: To assess the performance of a prenatal diagnostic service using quantitative fluorescent polymerase chain reaction (qf-PCR) and array comparative genomic hybridization (aCGH) as first line investigations. Second, to determine the incidence of copy number variants (CNVs) by indication for testing, with particular reference to ultrasound and biochemical parameters measured in combined first trimester screening. *Methods:* All women undergoing invasive prenatal testing at a specialist prenatal screening service in Sydney, Australia were included in the study. All samples had qf-PCR and aCGH (Agilent ISCA 8 × 60k array) processed by standard methodology. *Results:* In 1,049 cases, CNVs were reported in 156 cases (14.9%). Preliminary qf-PCR identified abnormalities in 104 of these cases. Of the remaining 52 cases, 20 could have been detected on karyotyping, leaving 32 cases (3.1%) with CNVs only detectable by aCGH of which 13 (1.2%) were pathogenic. Variants of unknown significance (VOUS) were only seen in 3 cases. Fetal structural abnormalities identified in the first trimester were the group most likely to be associated with pathogenic CNVs (11.8%). *Conclusions:* Combining qf-PCR and aCGH is an effective first-tier prenatal testing regime, without requiring conventional karyotyping. The VOUS incidence in this study is very low due to appropriate aCGH targeting and specific reporting criteria, which reduced the number of potentially difficult counseling encounters. Pathogenic CNVs are positively correlated with the presence of fetal structural abnormalities, but not with enlarged NT or abnormal first trimester serology results.

ASoC Oral 8
MONITORING BCR-ABL1 TRANSCRIPT LEVELS IN CHRONIC MYELOID LEUKEMIA PATIENTS BY PCR

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Droplet Digital PCR presents as a favorable technology for the monitoring of patients with leukemia in order to determine response to therapy, the presence of residual disease, and the emergence of relapse or resistance mutations. Initial ddPCR studies for monitoring of BCR-ABL1 transcripts in chronic myeloid leukemia (CML) patients correlates well with the in-house internationally standardized method at Canterbury Health Laboratories. Enormous efforts have been put into the international standardization of BCR-ABL1 levels, which relies on current real-time PCR technology. Current quality assurance programs continue to indicate wide variance among laboratories using different platforms. ddPCR gives an absolute measure of transcript, therefore transfer to ddPCR technology will negate the requirement for standards and therefore not only reduce the constant threat of contamination and false positives, but remove one variable in the quest for more uniform international standardization. We demonstrate that alternative BCR-ABL1 transcripts can be detected with the same fluorophore and that the assay can be easily adapted to include more than one control gene. By partitioning, this unique technology is more robust against preferential amplification of one target over another, in that amplification and reverse transcription occurs within each droplet and hence fewer competing transcripts. All these features will simplify testing and improve international standardization between laboratories, not only for monitoring BCR-ABL1 transcripts in CML patients, but also for other transcripts involved with other somatic cell conditions.

Selected Free Communication Oral 7
PREVALENCE OF FRAGILE X INTERMEDIATE / PREMUTATION ALLELES IN PATIENTS ASCERTAINED FOR ID / AUTISM, ATAXIA AND PREMATURE OVARIAN INSUFFICIENCY

Kathryn Friend[1], Evelyn Douglas[1], Rachael Catford[1], Anthony Correll[1], Eric Haan[1,2], Christopher Barnett[1,2], Chris Pearson[3], David Ketteridge[3], Phillip Thompson[4], Sui Yu[1]

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FMR1-related disorders include Fragile X syndrome, (FRAXA) FMR1-related primary ovarian insufficiency (POI) and Fragile X-associated tremor/ataxia syndrome (FXTAS). Fragile X syndrome (FRAXA) is the most common cause of inherited intellectual disability. Expansions of the CCG repeat in the 5's untranslated region of the FMR1 gene above a copy number of 200 CCG repeats is known to result in FRAXA (full mutation). Repeat expansions in the premutation range (55–200 CCG repeats) are associated with premature ovarian insufficiency (POI) in approximately 20% of carrier females and predisposes predominantly male carriers to Fragile X associated tremor and ataxia (FXTAS). Normal range alleles are approximately 5–44 repeat copies. We have reviewed our data for the last 10 years and summarise results for over 6,000 samples. Sample cohorts were separated into 3 groups: those referred for intellectual disability/autism/behavioral issues, premature ovarian insufficiency and spinocerebellar ataxia/ataxia. Allele distribution was analyzed and there was no significant difference between the 3 cohorts and alleles within the following CCG repeat ranges: 5–40, 41–45, 45–54 and 55–200. Notably, the number of POI and FXTAS positive cases (premutation allele) was much lower when compared to the published literature (4–6% and 2–4% respectively). The summary of these findings will be presented and discussed. Additionally, an interesting pedigree segregating for both an intermediate (49 CCG repeat allele, and premutation allele (57/59 CCG repeat copies) will be presented.

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ASoC Oral 10
IDENTIFICATION OF FETAL DNA IN MATERNAL PLASMA USING SEMI-NESTED PCR: A POSSIBLE APPROACH FOR NON-INVASIVE PRENATAL DIAGNOSIS

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Introduction: Prenatal diagnosis using fetal DNA is essential for detection of the fetal genotype in life-threatening genetic disorders such as thalassaemia. Individuals with beta-thalassaemia major require regular blood transfusions for survival. Epigenetic studies have revealed differences in methylation status in CpG sites between fetal and maternal DNA. The objectives of this study are to identify informative CpG sites in the beta-globin gene and develop a semi-nested methylation-specific PCR for amplification of chorionic villi (CV) DNA (trophoblasts that contribute to fetal DNA). *Methods:* Extracted DNA from 15 maternal blood and their respective CV samples was subjected to bisulfite conversion. The beta-globin gene containing three selected CpG sites and the beta-gene mutation at codon 41/42 was amplified. Amplicons were sequenced and the methylation status of each CpG site of the converted maternal (cM) and converted CV (cCV) DNA was compared. Three rounds of semi-nested PCR using three methylation-specific reverse primers were amplified in succession with a common forward primer. *Results:* Sequencing results confirmed the three CpG sites were hypermethylated in cM DNA and only partially methylated in cCV DNA. The semi-nested PCR showed amplification in 11 cCV DNA while no band was observed in all maternal DNA. The sensitivity and specificity of this approach is 73% and 100% respectively. *Conclusions:* Three rounds of semi-nested PCR on cM and cCV DNA has allowed the identification of circulating fetal DNA in maternal plasma. This technique may be utilized for non-invasive prenatal diagnosis of specific beta-globin gene mutations from fetal DNA in maternal plasma.

Molecular Genetics Society of Australasia Oral Presentations

MGSA Oral 1
ABNORMAL EXPRESSION OF SEX BIASED GENES IN PCDH19-FLE SUGGESTS A ROLE FOR NEUROSTEROID HORMONES

Jozef Gecz[1], Chuan Tan[1], Chloe Shard[1], Kim Hynes[1], Evelyn Douglas[2], Grant Buchanan[1], Enzo Ranieri[2], Carla Marini[3], Samuel Berkovic[4], Ingrid Scheffer[4]

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PCDH19-Female-Limited-Epilepsy (PCDH19-FLE) is an unusual X-linked disorder that primarily affects females. PCDH19-FLE encompasses a broad clinical spectrum from early infantile epileptic encephalopathy resembling Dravet syndrome to epilepsy with or without intellectual disability and behavioral problems, including autism. PCDH19-FLE is highly but not fully penetrant. We have tackled the questions of molecular pathogenesis of PCDH19-FLE by examining the transcriptomes of primary skin fibroblasts of PCDH19-FLE females ($n = 12$ and $n = 3$ age and passage-matched normal controls) and unaffected transmitting males ($n = 3$ and $n = 3$ age and passage-matched control males). We found that the expression of genes, which normally show sex (male/female) biased expression in this cell type, was significantly altered (observed = 43/94 vs. expected = 223/19223, $p = 1.09 \times 10\text{-}55$, two-tail Fisher's exact test). Follow-up studies (including additional skin fibroblast cell lines) validated at least ~60% of selected genes. From among several plausible biological candidates we focused our attention on the aldo-keto reductase family 1, member C1-3 (AKR1C1-3) genes, which play crucial role in neurosteroid hormone metabolism (which skin is endowed with). Additional support for steroid and neurosteroid hormone role in the pathology of PCDH19-FLE came from the age of onset (mean ~10 months) and offset (mean ~12.5 years) of epilepsy ($n = 100$ patients), both of which coincide with dramatically varying sex hormone levels (onset — after 'minipuberty' and offset — with the advent of puberty). This led us to postulate the neurosteroid hypothesis, which may explain PCDH19-FLE and opens realistic opportunities for targeted therapeutic interventions.

MGSA Oral 2
USP9X IS A NOVEL X-LINKED INTELLECTUAL DISABILITY GENE THAT REGULATES NEURONAL MIGRATION AND AXON GROWTH

Claire Homan[1], Lam Son Nguyen[1], Lucy Raymond[2], Charles Schwartz[3], Martine Raynaud[4], Stephen Wood[5], Jozef Gecz[6], Lachlan Jolly[1]

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Recently we contributed to the report of a large systematic resequencing of the X-chromosome in 208 families with non-syndromic X-linked intellectual disability (XLID). Coupled with the identification of copy number variants, the studies provided likely explanations for ~50% of cases. Among the single nucleotide variants reported, 3 unique changes found in separate families were mapped to USP9X, thus identifying it as a candidate XLID gene. The 3 variants (c.6278T>A p.Leu2093His; c.6469C>A p.Leu2150Ile; and c.7526delA p.Gln2509fs17*) segregated with ID within the families and alter highly conserved amino acids of the protein's C-terminus. Intriguingly, this region binds to another XLID gene product, Doublecortin, a microtubule associated protein involved in neuronal migration and axon growth.

To provide additional evidence that USP9X is a XLID gene, we knocked it out specifically in the embryonic brains of mice. Loss of Usp9x resulted in perinatal lethality, associated with abnormal cortical architecture, reduced hippocampal and corpus callosum volumes. Ex-vivo studies of Usp9x-null neurons revealed a 42% reduction of in-vitro migration ability, and a 43% reduction of axon growth. Proteomic analysis of isolated neurons highlighted disruption of microtubules and actin dynamics in the absence of Usp9x. While over-expression of human USP9X was able to partially rescue the migratory and axon defects of the knockout neurons, over-expression of the USP9X variants failed to do so. Together these data identify USP9X as a novel XLID gene that regulates neuronal migration and axon growth. Our findings are consistent with a model wherein USP9X may influence Doublecortin function during brain development.

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MGSA Oral 3
MUTATIONS IN *DEPDC5*: A MAJOR CAUSE OF FAMILIAL FOCAL EPILEPSY

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The majority of epilepsies are focal in origin, with seizures beginning in one region of the brain. The disorder Familial Focal Epilepsy with Variable Foci (FFEVF) is remarkable since family members have seizures originating from different cortical regions. FFEVF shows autosomal dominant inheritance in large pedigrees. To identify the gene for FFEVF we used a strategy of genome-wide linkage analysis followed by exome sequencing in two families, one Australian and one Dutch, which mapped to chromosome 22q12. We identified DEPDC5 mutations in the two families and subsequently in 5/6 published large families with FFEVF. We then sought to determine if mutations in DEPDC5 contribute more broadly to familial focal epilepsies. In our analysis of small families with non-lesional focal epilepsy, which were too small for a conventional clinical diagnosis, we found DEPDC5 mutations in approximately 12% (10/82). These findings reveal that DEPDC5 is a major cause of familial focal epilepsy. Shared homology with G protein signalling molecules and gene expression analyses suggest a role of DEPDC5 in neuronal signal transduction. The identification of DEPDC5 as a new epilepsy gene provides potential new drug targets, which is particularly important in focal seizures as these are often refractory to current medications.

MGSA Oral 4
UNRAVELLING THE MOLECULAR PATHOGENESIS OF *ARX* POLYALANINE TRACT EXPANSIONS

Cheryl Shoubridge, Kristie Lee, Tessa Mattiske, Jozef Gecz
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Intellectual disability (ID) is a highly prevalent disorder that affects 1–3% of the population, with a number of causative genes mapped to the X-chromosome. The Aristaless-related homeobox gene (ARX) encodes a transcription factor characterized by a homeodomain and four polyalanine (PolyA) tracts. ARX is indispensable for proper forebrain development and is a frequently mutated X-Linked ID gene. Expanded PolyA tracts account for over half of all mutations in Arx and clinically give rise to ID with or without epilepsy of varying severity. Mice modeling the human PolyA expansion (Arx(GCG)7) recapitulate many clinical features seen in humans. To dissect the molecular basis of PolyA expansions in vivo, we have analyzed mice modeling the two most frequent PolyA expansion mutations (Arx(GCG)7 and Arx432-455dup24)1. Interestingly, we did not observe protein aggregation in cells expressing Arx in contrast to in vitro studies. Instead, we noted a marked reduction in Arx protein abundance not only in the Arx(GCG)7 mice1, but in both mutant strains. This reduction could not be accounted for by a loss of cell mass or expression of Arx transcripts. To better dissect the mechanism underpinning the phenotypic differences due to PolyA expansions, we have begun to assess the transcriptional consequences of mutations in these mice. Our data indicate a selective effect of these mutations impacting on some but not all Arx downstream targets, potentially contributing to the manifestation of clinical features of the associated disease.

MGSA Oral 5
WHOLE EXOME SEQUENCING IDENTIFIES MUTATION IN THE RIBOFLAVIN TRANSPORTER GENE *SLC52A2* IN THREE AFFECTED CHILDREN WITH BROWN-VIALETTO-VAN LAERE SYNDROME

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There are around 7,000 known or suspected Mendelian disorders. Previously, genes causing Mendelian disorders have been identified through numerous strategies such as positional cloning and candidate-gene sequencing. More recently, new high-throughput genomics technologies have been developed and introduced, including autozygosity mapping and next generation sequencing (NGS) platforms, using either targeted, whole exome or whole genome analysis. These technologies were used widely to identify the genetic causes of many disorders, particularly the Mendelian disorders. We describe here a consanguineous Lebanese family with three affected boys with Brown-Vialetto-van Laere syndrome (BVVL) presented with deafness, peripheral neuropathy and optic atrophy. We performed exome sequencing in two individuals of this family (affected and unaffected). Exome capture was carried out using NimbleGen (44Mb) and the captured DNA was sequenced using an Illumina HiSeq 2000 Sequencer. Using this approach we identified a homozygous missense variation in the SLC52A2 gene at c.916G>A (p.Gly306Arg) in the three affected children. Sanger sequencing confirmed this mutation to be homozygous in the three probands, heterozygous on the four unaffected siblings and both parents. Radiolabelled riboflavin uptake studies in HEK293 cells confirmed that this mutation has a deleterious effect on riboflavin uptake. Thus, using exome sequencing, we have identified an autosomal recessive mutation in the SLC52A2 gene in a family with BVVL syndrome, highlighting the power of NGS technologies in disease gene discovery. Moreover, this discovery opens up the possibility of therapy with pharmacological doses of riboflavin to ameliorate or prevent disease progression if instituted early in the course of the disease.

MGSA Oral 6
TRENDS IN MOLECULAR GENETIC TESTING IN AUSTRALIA

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Background: As part of a review of current genetic testing arrangements in Australia, the Royal College of Pathologists of Australasia (RCPA) was contracted by the Department of Health and Ageing (DoHA) to conduct its second survey of genetic testing in Australia (the first conducted in 2006). The survey aimed to document medical genetic testing performed during 2011, by NATA-accredited cytogenetics, biochemical genetics and molecular genetics laboratories. Information was sought regarding testing volumes, types, purposes and funding. Data were collected by electronic means and then collated for analysis and comparison with 2006 molecular testing data. *Key findings:* Over 300,000 molecular genetic assays were performed in 2011. The majority of these were for diagnostic or screening purposes and funded by the States/Territories. Since 2006, there has been an increase in volume (2.8 fold) and range of molecular genetic tests performed annually; however, the proportion of assays funded by the Medicare Benefits Schedule (MBS) remains small. There is also concerning evidence of continuing inequitable access to molecular genetic testing across the country. Overseas testing remains as a small proportion of total assays

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requested nationally. *Conclusion:* The survey provides representative data that can be used to describe current practices and trends in medical genetic testing in Australia. Introduction of ongoing collection of national medical genetic testing data using a system that is shown to be valid and reliable may be worth considering.

MGSA Oral 7 (Workshop)
THE FIRST WHOLE EXOMES, THE GOOD, THE BAD, AND THE UGLY

Mark R Davis[1], Kym Mina[1], Gianina Ravenscroft[2], Royston W. Ong[2], Phillipa J. Lamont[3], Kyle S Yau[2], Elizabeth Thompson[4], Michael Fahey[5], Nigel G Laing[2], Richard J Allcock[6]

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The Lotterywest State Biomedical Facility Genomics based at Royal Perth Hospital received its first SOLID sequencing system in early 2011. The first whole exome sequence was generated in September 2011, and 18 months later the tally has reached 100 whole exomes sequenced. A number of challenges had to be overcome, but some outstanding results have been achieved that demonstrate the power of massively parallel sequencing (MPS) to revolutionize both the diagnosis of and research into genetic disease.

Diagnostically, MPS has proven particularly suited to the study of diseases with which large numbers of genes have been associated. An example is Charcot-Marie-Tooth (CMT) disease, for which 54 genes are currently known. Nine CMT families, for which the most commonly associated genes had been excluded, were analyzed by whole exome sequencing (WES), with definite or probable pathogenic mutations in known CMT genes identified in four. WES also enables the rapid translation of newly identified genes into the diagnostic setting. Within months of the first papers describing mutations in the DNAJB6 gene causing a form of limb girdle muscular dystrophy in six families, we were able to identify one of the same DNAJB6 mutations in a family with a similar phenotype. Finally, the identification of new disease genes has been accelerated dramatically with WES, and we currently have three new disease genes under investigation — two associated with foetal akinesia and one with mitochondrial disease.

MGSA Oral 8 (Workshop)
CUSTOM TARGETED RESEQUENCING METHODS IN A CLINICAL DIAGNOSTIC SETTING: GENETIC TESTING FOR EARLY INFANTILE EPILEPTIC ENCEPHALOPATHIES

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Early-onset epileptic encephalopathies are severe disorders of cognitive, sensory and motor development impairment. Genetic testing in this field is hampered by the highly heterogeneous nature of these disorders, with wide phenotypic spectra, overlapping clinical features and the involvement of multiple genetic loci. Due to the high costs and long turn-around times, traditional methods of molecular diagnosis are usually limited to a small number of candidate genes. Next-generation sequencing (NGS) provides an ideal platform for improving the genetic diagnosis of these disorders, by allowing a large number of genes to be tested simultaneously at a relatively low cost.

A panel of 52 genes has been chosen, based on their association with disorders of early-onset seizures, Rett syndrome, neuronal ceroid lipofuscinoses or other disorders with overlapping clinical features. Testing of these genes has been carried out using two targeted sequencing approaches (Agilent Haloplex Custom Target Enrichment kit and Illumina TruSeq Custom Amplicon). Both sets of libraries were then sequenced on an Illumina MiSeq Personal Sequencer. The Agilent Haloplex kit resulted in a better coverage of the target regions (in terms of bases covered) in all samples tested, compared to the Illumina TruSeq, although the percentage of reads on-target was higher for the latter. Next-generation sequencing technologies have the potential to transform the approach to which genetic testing of heterogeneous disorders may be undertaken. Further work is being carried out to evaluate the suitability and robustness of targeted sequencing approaches for clinical diagnoses.

MGSA Oral 9
ZEBRAFISH AS A MODEL SYSTEM FOR FUNCTIONAL INVESTIGATION OF VARIANTS IDENTIFIED VIA NEXT-GENERATION SEQUENCING IN GENETIC EYE DISEASE

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Developmental failure of the anterior eye structures including the lens, cornea, and iris can cause anterior segment dysgenesis (ASD), cataract, microphthalmia and/or glaucoma. Vision may be at risk with reduced corneal transparency or high tension glaucoma. The underlying genetic causes remain elusive in many cases. We have mapped a novel candidate disease gene from a balanced translocation patient with severe ocular anterior segment dysgenesis, microphthalmia and cataract. Additional predicted pathogenic variants in this gene have been identified in our ASD/cataract cohort by exome sequencing. We used zebrafish (*Danio rerio*) as a model system to test the function of this candidate disease gene in eye development. The spatial expression of the zebrafish orthologue was studied in eye development by in situ hybridisation and its expression was predominantly restricted to the lens. We designed splice-blocking morpholinos (MOs), and these were injected in early stages of zebrafish development. RT-PCR confirmed abnormal transcripts in the MO-injected embryos. The morphants had small eyes (microphthalmia) and irregular shaped lens with adhesion between the cornea and lens. These features were consistent with those seen in patients with abnormality of this gene. Our findings highlight the value of the zebrafish as a useful model for investigation of novel disease variants in genetic eye disease

MGSA Oral 10
CELL-BASED ASSAYS TO EXAMINE PATHOGENICITY OF NOVEL EYE DEVELOPMENT DISEASE GENES DISCOVERED THROUGH NEXT GENERATION SEQUENCING

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Application of next-generation sequencing has provided unparalleled opportunities for gene discovery, but there is a bottleneck in functional validation of the disease candidates. This study presents cell-based approaches used to elucidate the role of a novel candidate

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disease gene in eye development. The candidate disease gene was identified in a chromosomal translocation patient with a severe developmental eye disorder. Breakpoint mapping revealed transection of a gene with RAPGAP and PDZ domains which we hypothesized to be involved in cell-cell adhesion. Next-generation sequencing in an extended cohort of patients with developmental eye disease has identified other patients with likely pathogenic variants in this disease gene. Slide in situ hybridisation in the mouse revealed the candidate disease gene was highly expressed in the developing lens, consistent with the phenotypic features in the affected patients. Investigation in epithelial cell lines including MDCK, CaCo2, and HEK293 cells, revealed co-localisation of our candidate disease gene with E-cadherin, ZO-1 and F-actin, supporting a role for the encoded protein in cell-cell adhesion. CaCo2 cells were used to generate cysts in a 3-dimensional matrix, and shRNA knockdown of our candidate disease gene revealed abnormal cyst formation. There was aberrant multi-layering of the epithelial cells consistent with abnormal morphogenetic appearances in lens of knockout mice we have also generated for investigation of this gene. Our work emphasizes the utility of cell-based approaches for functional analysis of candidate disease genes affecting the lens and developing eye identified through next-generation sequencing approaches.

MGSA Oral 11
MODELING ASPECTS OF WILLIAMS-BEUREN SYNDROME IN MICE: THE ROLE OF A NOVEL EPIGENETIC REGULATOR IN THE CRANIOFACIAL AND NEUROLOGICAL FEATURES

Stephen Palmer[1], Cesar Canales[1], Paulina Carmon-Mora[1], Jocelyn Widagdo[1], Ann Wong[1], Gary Housley[1], Pritinder Kaur[2], Anthony Hannan[3], Peter Gunning[1]

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Williams-Beuren syndrome (WBS) is a neurodevelopmental disorder resulting from a hemizygous microdeletion within chromosome 7q11.23 involving 28 genes. Genotype-phenotype correlations in patients with atypical deletions have mapped the typical craniofacial dysmorphologies, hypersociability and visuospatial problems to a pair of genes that encode the evolutionarily related transcriptional regulators GTF2IRD1 and GTF2I.

The gene GTF2IRD1 was originally cloned and characterized in our laboratory and we have generated Gtf2ird1 knockout mouse lines that show some striking similarities to aspects of the human disease. Similar to WBS patients, knockout mice have large lips and this phenotype correlates with the pattern of Gtf2ird1 expression in the developing face. Gtf2ird1 is also expressed in discrete brain regions and sensory structures that correlate with other abnormalities in the knockout mice, including defects of motor coordination, hearing, exploratory drive and anxiety. Expression profiling in knockout brain tissue supports a role for GTF2IRD1 in target gene repression and the epigenetic control of experience-induced gene activity.

To understand how this may work, our molecular analysis indicates that GTF2IRD1 negatively auto-regulates its own allele though direct DNA binding, and utilizes protein interaction domains to cooperate with other DNA binding proteins. GTF2IRD1 then interacts with an assortment of chromatin modifying proteins that explain its role in epigenetic gene silencing. The GTF2IRD1 protein is also subject to tight control of abundance and activity through SUMOylation and ubiquitin-mediated proteasomal degradation. Together, these data support the role of GTF2IRD1 in WBS and start to unpick the molecular and cellular basis of the craniofacial and neurological features.

MGSA Oral 12
THE MIR17-92 MICRORNA CLUSTER AND SPONTANEOUS MALFORMATION

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A duplication of the miR17-92 miRNA cluster was detected in an individual with pre-axial polydactyly and craniofacial dysmorphism. We used a chick embryo overexpression system to determine whether duplicated miR17-92 was responsible for these birth defects. We found that a proportion of infected embryos exhibited additional digits, suggesting that this was the case. However, we also saw a range of more complex limb malformations including duplications of entire limbs and partial duplication of the limb with otherwise normal skeletal elements. In addition to limb phenotypes, we also see a range of abnormalities involving other tissues including exencephaly, gastroschisis, superficial papillae extending from the body wall, adhesion of embryonic membranes to the flank/limbs and skin spurs. Most affected embryos have only a single malformation and many embryos overexpressing miR17-92 appear to develop normally. This range of dysmorphology involves diverse cell types that do not appear to follow any clear pattern. The broad range of phenotypes suggests that overexpression of these miRNAs does not produce any one specific birth defect but creates a propensity for birth defects, leaving the embryo susceptible to diverse structural abnormalities. We hypothesize that miRNAs encoded by these miRNA clusters regulate a surveillance system which normally suppresses spontaneous structural anomalies arising stochastically throughout development. Further, we hypothesize that repression of this surveillance system through dysregulation of miR17-92 family miRNAs is responsible for a range of apparently spontaneous human birth defects.

Australian Society of Genetic Counsellors Oral Presentations
ASGC Oral 1
HUNTINGTON DISEASE FOR THE GENETIC COUNSELOR

Sandy Macleod
Health Sciences Centre, University of Canterbury, Christchurch, New Zealand

Abstract not provided at time of printing.

ASGC Oral 2
GENETIC HEALTH SERVICE PROVISION FOR INDIGENOUS AUSTRALIANS: A QUESTION OF CULTURE AND DIFFERENCE

Lyndon Gallacher[1], Margaret Sahhar[2], Ivan Macciocca[2], Emma Kowal[1]

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It is well established that cultural factors impact on the provision of genetic health care in a range of populations. Indigenous populations are thought to have particularly low levels of access to genetic health services, and cultural issues may be a contributing factor. We present data from the first study of genetic health service provision to Indigenous Australians. This qualitative study aimed to identify elements of culturally competent genetic health service provision for this population group. Twelve semi-structured interviews were conducted with genetic counselors and clinical geneticists from around Australia who had experience delivering services to Indigenous Australians. Participants were asked to describe their experiences and comment on collective cultural needs they identified, as well as

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training and resources for health professionals working with Indigenous patients. Interviews were audio-recorded and transcribed with thematic analysis conducted on the data. The findings show that participants were reluctant to generalize the needs of Indigenous peoples. Some participants asserted that Indigenous peoples have needs that differ from the general population, while others felt that there were no collective cultural needs, instead advocating an individualized approach. However, being flexible and practical, taking time to build rapport, recognizing different family structures and decision-making processes, as well as other socio-economic factors, were all identified as important factors in participants' interactions with Indigenous patients. Indigenous support workers and hospital liaisons were seen as valuable for service provision. This research has important implications for policy, training and practice, and these issues will be discussed.

ASGC Oral 3
EXPLORING THE GENETIC COUNSELING AND INFORMATION NEEDS OF UNAFFECTED MALES IN FAMILIES WITH X-LINKED INTELLECTUAL DISABILITY

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While the reproductive genetic counseling needs and perception of risk of females within X-linked Intellectual Disability (XLID) families are well reported there are no comparable studies of unaffected males within XLID families. These males may be overlooked because of their low reproductive risk. Anecdotally, it has been observed these males are often unaware of the X-linked pattern of inheritance in the family and perceive they are at increased risk of having a child with intellectual disability (ID). A qualitative pilot study was undertaken in collaboration with NSW Genetic Education to explore the genetic and reproductive counselling needs of unaffected males in XLID (non-fragile X) families. Six unaffected males, who had recent contact with the Genetics Of Learning Disability Service, agreed to a 30-minute telephone interview by an independent interviewer. The transcripts were coded by Nvivo to identify common themes. Over half the males had incomplete or inaccurate knowledge of X-linked inheritance and most had significant concerns about their risk of having a child with ID. Most wanted accurate information from a health professional to enhance their confidence and their partner's confidence in the information being disseminated within the family, especially in regards to their low risk of having a child with ID. Other common themes to emerge were the significant burden of having a lived experience of ID in their family and the associated impacts and challenges. This explorative study provides recommendations to address the unique and unmet genetic counseling and information needs of unaffected males within XLID families.

ASGC Oral 4
PARENTAL EXPERIENCES OF LIVING WITHOUT A DIAGNOSIS FOR CHILDREN WITH UNEXPLAINED SYNDROMES

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Rapid advances in genetic testing have the potential to provide a diagnosis for individuals in whom no underlying genetic cause had previously been identified. The aim of this study was to understand how parents experience living without a definitive diagnosis for their child's dysmorphic features and developmental disability, and to explore how they value a diagnosis in the context of the future availability of new genetic technology.

As limited prior research has been conducted in this area, a qualitative phenomenological approach was taken. Semi-structured interviews were used to explore the experiences of ten parents of nine children living with ongoing diagnostic uncertainty. Interviews were transcribed verbatim and data were coded into themes through thematic analysis.

Parents provided in-depth recollections of the difficult process of syndrome diagnosis and the distress experienced at the physical scrutiny of their child during a dysmorphology examination. Parents expressed ambivalence regarding the value of a genetic diagnosis for their child. While acknowledging the benefits of using new genetic technologies, some parents were wary of pursing a diagnosis that could challenge coping strategies that had been established around a lack of diagnosis. A diagnosis could reveal new prognostic information that might threaten parents' hopes for the future.

Findings highlight the complexity in parents' experiences and perspectives. Parents simultaneously perceived benefits and risk in attaining a diagnosis. A conceptual framework is proposed to describe the relationship between the development of resilience in the face of no diagnosis and resulting ambivalence with respect to genetic testing technologies. The results raise important considerations for genetic counseling practice in relation to future clinical application of new genetic testing technology to resolve diagnostic uncertainty.

ASGC Oral 5
CO-COUNSELING: DO WE KNOW WHAT WE ARE DOING AND WHAT IS OUR ROLE?

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Co-counseling is one teamwork model used in healthcare and involves two or more health professionals conducting the majority of a client consultation together. While this model is commonly used in the current practice of genetic counseling there has been limited research exploring the use of co-counseling, aside from a pilot study undertaken in 2005.

A qualitative study was undertaken with genetic health professionals in Victoria to explore their understanding and experiences of co-counseling. Two focus groups were conducted with genetic counselors and clinical geneticists. Participants discussed their understanding of the term 'co-counseling' in relation to genetic counseling, their experience and perception of how clients perceive the model, their understanding of their own role and their views on training to undertake co-counseling. Other areas explored included the criteria for deciding when to use co-counseling and the advantages and disadvantages of using such a model in the delivery of genetic services.

The findings suggest that genetic health professionals are uncertain about the purpose of co-counseling and their own role in the team. This uncertainty was more common among genetic counselors than clinical geneticists and contributed to a lack of confidence in the role of genetic counselors in co-counseling. Despite this uncertainty, most genetic health professionals valued utilising co-counseling in their practice. These findings will be discussed along with their significant implications for the current practice of genetic counseling and the training of genetic counselors and clinical geneticists.

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ASGC Oral 6
DIFFICULT DECISIONS: A MULTIDISCIPLINARY APPROACH TO GENETIC COUNSELING FOR HAEMOGLOBINOPATHIES IN AN ANTENATAL SETTING

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We conducted an audit of prenatal diagnostic testing for hemoglobinopathies conducted in Victoria from 1996 to 2012. Diagnostic testing became centralized to the Clinical Genetics Laboratory at Southern Health in 1996 with 25 diagnostic prenatal tests being performed. Since then, the numbers of diagnostic tests conducted have fluctuated around a mean of 31.95 per annum, with 25 in 2001, and 30 in both 2006 and 2011. 2007 and 2008 both had 40 CVSs for haemoglobinopathy performed. These reflect an ongoing need for genetic counseling for prenatal testing in hemoglobinopathies.

The need for lifelong treatments for transfusion-dependent patients present challenges for parents considering antenatal testing and continuation or termination of an affected pregnancy, both medically and socially. However, improvements in treatments and increased public awareness of hemoglobinopathies have led to a changing patient perspective on what was once considered a devastating diagnosis. For some couples this, often coupled with variability of severity of symptoms in an increasing array of genotypic combinations, has made the decision as to whether to test or to continue an affected pregnancy more difficult. A multidisciplinary approach involving clinical, social work and counseling staff provides an effective framework to promote informed decision-making for people contemplating testing.

We present two cases highlighting the difficult decisions faced by some prospective parents that involve not just medical considerations, but often complex social situations that become significant with the chronic nature of hemoglobinopathies: one involving a woman with beta-sickle cell disease who underwent prenatal diagnosis and opted to continue with an affected pregnancy; and a second case involving a couple at risk of having a baby with an unpredictable but possibly severe anemia who held strong religious views against both termination and blood transfusion. Both couples had to balance social and religious views with the ongoing demands of possibly caring for a child with a severe hemoglobinopathy in difficult social frameworks.

ASGC Oral 7
THE INTRODUCTION OF THE INTAKE ASSISTANT ROLE IN A FAMILIAL CANCER CENTRE

Alisha McLauchlan, Emma Swain, Jessica Taylor, Kirsty Mann, Geoff Lindemann, Michael Bogwitz
Melbourne Health, Melbourne, VIC, Australia

Referrals to The Royal Melbourne Hospital Familial Cancer Centre (RMH FCC) have increased by up to 25% each year since 2009, placing strain on both genetic counselors and administration staff. The role of the Intake Assistant was therefore developed to help with the increased workload. This role has become vital to the efficient functioning of the FCC. Intake Assistants are responsible for gathering the family history information prior to an appointment, which is a labor-intensive process. Their role includes: introducing our service to individuals referred, gaining a preliminary understanding of client expectations, gathering family data, triaging clients into the most suitable multidisciplinary clinic, and flagging clients who may require additional support.

This is believed to have benefits for the service by guiding clients through the information-gathering stage, potentially increasing the chance a client will attend an appointment, while decreasing the workload for other staff members. In addition, the employment of staff whose sole focus is on intake has allowed the RMH FCC to evaluate this method of client intake. We have recruited Intake Assistants who are concurrently undertaking a Master of Genetic Counselling. With appropriate planning, supervision, and role clarification, the Intake Assistants have an opportunity to develop their active listening and telephone skills and confidence, prior to securing employment as a genetic counselor. We will present the experience of the Intake Assistants in our clinical service, particularly the benefits for genetic counselors, the administration team as well as the intake assistants themselves.

ASGC Oral 8
DETERMINING GILLICK COMPETENCE IN MINORS UNDERGOING PREDICTIVE TESTING FOR AN INHERITED CARDIAC DISEASE

Lauren Hunt, Mathew Wallis, John Atherton, Stephen Stathis, Julie McGaughran
Queensland Health, Brisbane, QLD, Australia

The Queensland Cardiac Genetics Clinic is a multidisciplinary service encompassing cardiology, genetics, and in some cases, psychiatry. Since the clinic's conception at the Royal Brisbane and Women's Hospital in 2007, over 550 patients have been seen. Approximately 7% of the patients seen were under the age of 18 at the time of their appointment. In cases where a minor presents for predictive testing for an inherited cardiac disease, a pediatric psychiatrist referral is often made. This provides a second independent assessment of the minor's Gillick competence to consent to predictive testing. This presentation will review the patient cohort who had been offered a pediatric psychiatrist appointment. We will report on the outcomes of these appointments in determining Gillick competence, whether the minor proceeded with testing, and on some of the positive and negative aspects of predictive testing experienced by these minors and their families.

ASGC Oral 9
GENETIC COUNSELING AND PRENATAL MICROARRAYS: ORDER OUT OF CHAOS

Susan Fawcett[1], Lydia Gaffney[1], Erica Brown[1], Jacqueline Greenberg[1], Lisa Gordon[1], Melody Menezes[2], Susan Fawcett[1]

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The introduction of SNP Microarray into the prenatal testing arena has been the focus of much discussion among specialists working in the area, including genetics, obstetrics and pediatrics. The focus of concern has been around our ability to effectively counsel couples following the detection of a CNV or inadvertent pathogenic finding. While it is now accepted that this technology is more effective in detecting pathogenic chromosomal changes than standard G banded cytogenetic analysis, it is the presence of variants of unknown significance (VOUS) that pose challenges for genetic counseling. Of ethical concern is whether disclosing these VOUS creates unnecessary or unwanted anxiety for the client. We will present key case studies in which we will highlight the counseling issues for the client and the counselor, and reflect on strategies employed to enable the couple to make meaning of the information and to facilitate decision-making.

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ASGC Oral 10
CANCER GENETICS: APPRECIATION OF PITFALLS IN COUNSELING

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Professional counseling for individuals at risk for hereditary forms of cancer implies supporting them to make an eventual decision with regard to genetic testing, additional management options, and communication to important others. The counselor ought to envisage six distinguished perspectives that enables sound counsellng. The first perspective concerns the client-centered, non-directive approach and establishing a good relationship. In addition, the patient may count on the counselor's awareness of the cognitive-rationalistic, psychodynamic, family, behavioristic and existentialistic perspectives. However, isn't this looking for the impossible? To keep up courage, we as professionals need to acknowledge and appreciate the great variety of pitfalls in our work.

ASGC Oral 11
A RANDOMISED CONTROLLED TRIAL OF A GENETIC COUNSELING INTERVENTION TO ENHANCE FAMILY COMMUNICATION: THE GIF STUDY

Jan Hodgson[1,2], Sylvia Metcalfe[1,2], Hannah Brown[1,2], Clara Gaff[3,2], Jane[1,2]

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When a person receives a diagnosis of a genetic condition for themselves or their child, many at-risk relatives remain unaware of this information. Previous data suggest that a genetic counseling intervention, delivered post consultation, may result in increased access to genetic services by family members. The NHMRC-funded GIF study aimed to assess the effectiveness of intense genetic counseling follow-up on numbers of at-risk relatives utilizing genetics services.

Participants (probands) ($n = 95$) were recruited when attending a genetic service for diagnosis or genetic testing and randomized into an intervention or control arm. The control group ($n = 50$) received usual care while the intervention group ($n = 45$) received three telephone counseling interventions. Twelve genetic counselors were trained in delivery of the GIF counseling intervention and phone calls were audiotaped, transcribed and analyzed. After 18 months, clinical files were audited to look for differences in the proportion of at-risk relatives who contacted genetics services. Participants were surveyed to explore their experiences of family communication and GIF counselors participated in a focus group about the intervention process.

Data analysis is ongoing but preliminary findings suggest that the GIF genetic counseling intervention, specifically designed to enhance family communication: (1) Remains congruent with principles of genetic counselling practice; (2) Can be delivered successfully by different counselors; (3) Is well received by clients; (4) Can improve the ability of clients to communicate genetic information effectively. Findings have implications for health professionals who wish to assist clients in effectively communicating new genetic information to at-risk relatives.

ASGC Oral 12
AUSTRALASIAN GENETIC COUNSELORS' VIEWS TOWARDS OBSERVING CANCER CARE AS A FORM OF INTERDISCIPLINARY EDUCATION: RESULTS OF A SURVEY OF THE ASGC

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Genetic counselors in Australasia typically work in hospitals and participate in interdisciplinary clinical teams. However, in their training and workplace, genetic counselors seldom have exposure to the medical environments in which their clients receive their medical investigations and treatment. After successfully piloting a program for genetic counselors to observe specialists' consultations and medical procedures most specific to their specialty area, we wished to investigate further by exploring the perceived benefit, interest, and feasibility of such a program being undertaken as a part of professional development for genetic counselors. A survey of members of the Australasian Society of Genetic Counsellors was conducted to: (1) Gain insight into the extent that cancer genetic counsellors have exposure to and familiarity with the clinical aspects of patient care and roles of other interdisciplinary team members; (2) Understand how genetic counselors most commonly acquire this knowledge; (3) Explore views towards the perceived benefits of the developed program; (4) Obtain views about the feasibility the program in the workplace.

We present the results of this survey. Of note, the results highlighted that genetic counselors most often obtain knowledge about medical procedures and consultations with other specialists from second-hand sources, such as anecdotal reports from patients and fact sheets, while few reported first-hand knowledge (experience of observing in person). Over 95% of respondents expected that the program described would be a beneficial part of their professional development and almost 90% expected the program is potentially feasible in their workplace.

ASGC Workshop
GENETIC COUNSELING FOR ADOLESCENTS AND YOUNG ADULTS

Mary-Anne Young, Lucy Holland, Kate Thompson
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Advances in genetics have led to an ever-increasing repertoire of options to improve health, modify genetic predisposition and save lives. Traditionally, adults have comprised the main group presenting for genetic counseling and testing. Genetic counselors support people through the genetic counseling and testing process. They are well versed with providing adults with genetic counselling, having been primarily trained in working within an adult-centered model of care. However, with advances in knowledge of genetic risk for a number of diseases, increasing numbers of adolescents and young adults (AYAs) aged 15–30 years are accessing genetic services across Australia. Youth friendly genetic counselling is a new and emerging field defined by the complexity of the AYA life-stage, which involves changes in every realm of human functioning. This field is characterized by unique implications of genetic counseling and testing on AYA psychosocial wellbeing, ethical issues about the capacity of AYAs to consent and the impact of development on adherence to disease management strategies.

The ONTrac at Peter Mac Victorian Adolescent & Young Adult Cancer Service in collaboration with the Familial Cancer Centre (FCC) at Peter Mac have developed a world first Youth Friendly Model of Genetic Counselling. The theoretically and practically

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based model aims to improve outcomes for AYAs having genetic counselling and testing and best support genetic counsellors in the delivery of care to young people and their families.

The workshop will be interactive and: (1) present the developmental stages of AYA's (specific to cognitive development and capacity for consent); (2) describe the process of genetic counseling for AYA's and how this differs from adult based practice; (3) discuss case scenarios to highlight and practice skills and strategies specific to working with AYAs

Australian Association of Clinical Geneticists Oral Presentations

AACG Oral 1
AN EYE ON THE GENOME: WHAT WILL BE THE IMPACTS OF NGS ON CLINICAL PRACTICE?

Graeme Black

Genetic Medicine, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

Next generation sequencing (NGS) technologies have revolutionized gene discovery programs. Such high throughput parallel sequencing platforms also promise to revolutionize clinical practice in an unprecedented fashion. We have developed and are now delivering, on a service delivery basis, gene panels for retinal dystrophy (105 genes) and congenital cataract (115 genes). Using over 12 months of experience of delivering these services, this talk will examine the utility of NGS for diagnosis of heterogeneous ophthalmic disorders. This will discuss the broader impacts including: consent and ethical issues; economic issues including the effects on current manpower /work load; the problems of incidental findings and variants of unknown significance; bioinformatics approaches and training; alteration to clinical diagnostic pathways.

AACG Oral 2
NEW SYNDROME OF ECTRODACTYLY AND LETHAL PULMONARY ACINAR DYSPLASIA ASSOCIATED WITH HOMOZYGOUS *FGFR2* MUTATION IDENTIFIED BY EXOME SEQUENCING

Christopher Barnett[1,2], Hashinee Weraduwage[1,3] Nicholas Manton[2]

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Casamassima-Morton-Nance syndrome (CMN) is a disorder with considerable clinical overlap with spondylocostal dysostosis but with additional features of anal and urogenital abnormalities. Since the first cases were described in two Mennonite children in 1981, there have been 5 other reported cases of CMN syndrome. Here we present a further case of CMN syndrome with characteristic vertebral and rib abnormalities, urogenital abnormalities, anal atresia and with additional features of hand abnormalities and a multicystic dysplastic kidney not described before. To the best of our knowledge this is the seventh case of CMN syndrome reported to date.

The mother was a healthy G3P2 Caucasian woman in a non-consanguineous relationship with 2 healthy children. Nuchal translucency was increased (3.1 mm) at 12 weeks gestation. The morphology ultrasound scan done at 20 weeks gestation identified a thickened nuchal fold, multiple vertebral segmentation anomalies, a left multi-cystic dysplastic kidney, marked pelvicaliectasis on the right and hydroureter with abnormal renal parenchyma. There was also a small stomach and severe oligohydramnios. Following termination of pregnancy at 22 weeks gestation a limited autopsy examination was performed. This revealed dysmorphic coarse facial features, marked scoliosis, a short webbed neck, large broad hands with a prominent gap between the index and middle fingers bilaterally, ulnar deviation of the left hand, bilateral talipes, ambiguous external genitalia and anal atresia. Routine chromosome analysis revealed a normal 46,XY male karyotype.

The genetic etiology of CMN syndrome remains unknown; however, autosomal recessive inheritance is likely. Exome sequencing is being performed on this current case in the hope of identifying the cause.

AACG Oral 3
VAN MALDERGEM SYNDROME IS CHARACTERIZED BY DEFECTIVE NEUROEPITHELIAL ADHESION LEADING TO DYSREGULATION OF NEUROPROGENITOR CELL PROLIFERATION AND DIFFERENTIATION

Stephen Robertson[1], Silvia Cappello[2], Mary Gray[1], Andrew Sutherland-Smith[3], Sahar Mansour[4], Jacques Michaud[5], David Markie[1], Myriam Srour[5], David Chitayat[6], Magdalena Goetz[2]

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The orchestration of proliferation and differentiation of neuronal stem cells prior to their radial migration to the cerebral cortex is central to brain development in humans. Periventricular neuronal heterotopia (PH), the mislocalization of grey matter centrally within the brain, can indicate a failure of neuronal progenitors to negotiate some aspect of this developmental process. Using combinations of autozygosity mapping and exome sequencing, bi-allelic mutations in genes encoding a pair of giant cadherin proteins that operate as a receptor-ligand pair are shown to lead to van Maldergem syndrome (VMS; MIM 601390), a recessive multiple malformation syndrome in humans characterized by intellectual disability, craniofacial, auditory, renal, skeletal and limb malformations in addition to a partially penetrant PH phenotype. In 7 unrelated families with the disorder, both truncating and missense mutations were characterized, indicating a loss of function mechanism in the genesis of VMS. To understand the mechanism behind compromised cadherin receptor-ligand engagement in the genesis of impaired neuronal migration in the mammalian brain, we employed in utero shRNA directed knockdown of both genes in mouse embryos. A reduction in expression of both genes resulted in an increase in neuroprogenitor cell number combined with a block in differentiation of neuronal precursors, resulting in the heterotopic accumulation of cells in the subcortex. These findings, which are reminiscent of the human phenotype, underscore the existence of links between neuroepithelial layer integrity and the control of proliferation and differentiation of neuronal precursors during human cortical development.

AACG Oral 4
CLINICAL CHARACTERISATION OF A NEW DISEASE GENE FOR NEMALINE MYOPATHY

Sarah Sandaradura[1], Michaela Kreissl[1], Leigh Waddell[1], Emily Todd[2], Gianina Ravenscroft[2], Carina Wallgren-Pettersson[3], Daniel MacArthur[4], Nigel Laing[2], Kathryn North[5], Nigel Clarke[1]

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Nemaline myopathy (NM) is characterized by generalized muscle weakness with involvement of facial, bulbar and respiratory muscles and nemaline bodies on muscle biopsy. Pathogenic mutations have been described in 8 genes to date and there is evidence of further

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genetic heterogeneity. Whole-exome sequencing on two siblings with NM and non-consanguineous parents identified a new disease gene for this condition. Through collaborative research, compound heterozygous or homozygous nonsense or frame-shift mutations have been identified in a further 13 families. Characterization of affected individuals has demonstrated that most patients have profound congenital weakness and hypotonia that causes respiratory failure and death in the neonatal period. A distinctive pattern of nemaline bodies, found in several patient biopsies on electron microscopy, may be a useful diagnostic indicator of this condition. Western blotting studies indicate most mutations associated with severe congenital weakness lead to loss of protein expression in skeletal muscle. Expression of mutant protein was detected in a proband with a less severe phenotype, suggesting expression of mutant protein may reduce disease severity.

AACG Oral 5
AN OPEN LABEL CLINICAL PILOT STUDY OF RESVERATROL AS A TREATMENT FOR FRIEDREICH ATAXIA

Eppie Yiu[1,2,3], Geneieve Tai[1], Roger Peverill[4], Kate Lee[1], Kevin Croft[5], Trevor Mori[5], Barbara Scheiber-Mojdehkar[6], Monika Praschberger[6], Adam Vogel[1,3], Gary Rance[3], Sarah Stephenson[1], Paul Lockhart[1], Joseph Sarsero[1], Creina Stockley[7], Andrew Churchyard[3], Marguerite Evans-Galea[1], Monique Ryan [1,2,3], LC Corben[1,4], MB Delatycki[1,3,8]

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Background: Friedreich ataxia (FRDA) is due to a triplet repeat expansion in the FXN gene, resulting in deficiency of the mitochondrial protein frataxin. Resveratrol is a plant-derived polyphenol. It was identified to increase frataxin expression in cellular and mouse models of FRDA, and has antioxidant properties. *Methods:* This trial evaluated the effect of two different doses of resveratrol on lymphocyte frataxin levels over a 12-week period in individuals with FRDA. Secondary aims evaluated the effect on FXN mRNA, oxidative stress markers and clinical measures of disease severity. Safety and tolerability were studied. *Results:* 24 participants completed the study; 12 received low-dose resveratrol (1 g daily) and 12 high-dose resveratrol (5 g daily). Lymphocyte frataxin levels did not change in either dosage group [low dose group change: 0.08 pg/Œ°g protein (95% CI -0.05, 0.21, $p = .21$); high dose group change: 0.03 pg/Œ°g protein (95% CI -0.10, 0.15, $p = .62$)]. Improvement in ataxia was evident in the high-dose group (change in International Cooperative Ataxia Rating Scale, ICARS -1.9 points, 95% CI -3.1, -0.8, $p = .004$) but not the low-dose group (change in ICARS -0.3 points, 95% CI -3.2, 2.6, $p = .80$). Significant improvements in hearing and speech were demonstrated in the high-dose group. A significant decrease in the oxidative stress marker plasma F2-isoprostanes occurred in the high-dose group. No serious adverse events were recorded. Gastrointestinal side effects were a common, dose-related adverse event. *Conclusions:* This trial provides evidence for high-dose resveratrol as a potential disease-modifying therapy for FRDA. A placebo-controlled trial is required to assess its benefits further.

AACG Oral 6
THE NEED FOR CAREFUL DIAGNOSIS OF CONGENITAL MYASTHENIC SYNDROMES WITH SECONDARY COMPLEX I DISORDERS

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Congenital myasthenic syndromes (CMS) are a family of inherited neuromuscular disorders characterized usually by muscle weakness and easy fatigability. There is considerable phenotypic overlap between CMS and mitochondrial myopathies, which may include ptosis, ophthalmoplegia, respiratory and skeletal muscle weakness and fatiguability. Here we report two patients with CMS and secondary complex I (CI) deficiency. For patient 1 (P1) whole exome sequencing (WES) was undertaken to identify the basis of the CI deficiency, which resulted in the identification of a compound heterozygous mutations in the COLQ gene, which is associated with CMS. In patient 2 (P2), also with reduced CI activity, an out-of-frame dystrophin mutation and a homozygous DOK7 mutation, which has been previously reported as pathogenic leading to CMS, were identified. The DOK7 mutation has been also identified in siblings and a cousin of P2; however, P2 had a more severe phenotype and died at the age of 7 months, possibly exacerbated by the dystrophin defect. Mutations in the nuclear encoded CI or related genes were not found in either patient, suggesting that that the CI deficiency might be a secondary artefact due to the primary COLQ and DOK7 abnormalities. CMS are rare but important to diagnose as they can be fatal but are often treatable. The apparent functional abnormality of CI adds further complexity, and diagnosis of CMS should be considered even when the clinical presentation points towards a mitochondrial myopathy. Electrophysiological tests such as repetitive nerve stimulation and single fibre electromyography may help in a clearer diagnosis.

AACG Oral 7
CHROMOSOME ABNORMALITIES DETECTED BY SNP MICROARRAY IN A COHORT OF 28 INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA

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Congenital diaphragmatic hernia (CDH) is a relatively common birth defect, affecting up to 1 in 4,000 live births. CDH can occur in isolation or be associated with a recognized syndrome, a chromosome abnormality, or a non-syndromic constellation of major malformations, notably congenital heart disease. The adoption of array-based platforms as the first-line chromosome investigation in infants with congenital abnormalities has resulted in the identification of numerous copy number variants (CNVs) in infants with CDH.

We report on the chromosome abnormalities detected by SNP microarray analysis in a cohort of 28 infants with congenital diaphragmatic hernia treated at the Royal Children's Hospital in Melbourne, Australia. Of these, 9 (32%) had a microarray abnormality. Seven of these (25%) were judged to be pathogenic or likely to be contributing to the pathogenesis of CDH, including two cases of mosaic Trisomy 9, a chromosome 9q2.31q22.3 microduplication, two chromosome 22q11.21 microdeletions, a 2q35 deletion and a 15q11.2 deletion.

The routine use of molecular karyotyping increases diagnostic yield in the CDH group. An apparently isolated defect is not a predictor for absence of chromosome abnormality. Furthermore, the identification of specific CNVs in this group of patients offers insights into the genetic mechanisms underlying the aetiology of

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CDH and we speculate on the role of various candidate genes in the pathogenesis of this multifactorial condition.

AACG Oral 8
COPY NUMBER VARIANTS CONTRIBUTING TO AUTISM IN AUSTRALIA

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Background: Autism spectrum disorders (ASD) are defined by the triad of social deficits, communication impairments and restricted interests or repetitive behavior. Recent advances in molecular genetics, specifically the introduction of high resolution molecular karyotyping, have improved etiological diagnosis rates from approximately 4% to 15–20%. *Aim:* To investigate the rate of causative copy number variants (CNVs) in children with ASD in Australia. *Methods:* Data was obtained from two sources: (1) an existing Autism Register in the Barwon Region of Victoria, and (2) The Western Australian Autism Biological Registry. Individuals with known chromosomal etiology were excluded. Karyotypes were performed using either the Illumina HymanCytoSNP-12 v.2.1 or the Affymetrix Genome-Wide Human SNP Array 6.0. CNVs were reported if >0.2Mb; however, smaller variants were reported if gene content was relevant to ASD phenotypes. *Results:* Data was analyzed from 428 individuals (207 Barwon; 221 Western Australian). We identified CNVs in 118/428 (27.6%) of cases. 21/428 (4.9%) demonstrated either clearly pathogenic or recurrent CNVs that have previously been reported in association with ASD. 23/428 (5.4%) had clearly benign CNVs and in 73/428 (17.1%) CNVs of uncertain clinical significance were identified. A clinically significant CNV unrelated to ASD was identified in 1/428 (0.2%). *Conclusions:* Our Australian figures are at the lower end of the range found in recent international studies, possibly reflecting the community ascertainment of our cohorts. Classification of CNV pathogenicity presents an evolving challenge to clinicians and molecular scientists. High resolution molecular karyotyping is a first line investigation for individuals with ASD.

Selected Free Communications

Oral 1
THERE ARE NO HARD AND FAST RULES: GENETIC HEALTH PROFESSIONALS' VIEWS AND RECOMMENDATIONS FOR PARENTS TO DISCLOSE CARRIER STATUS TO THEIR CHILDREN

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There is a general consensus in genetic counseling that sharing of genetic information within families and disclosure of genetic risk by parents to their children is important. In the area of carrier testing in children, a small number of studies have assessed health professionals' views on the age at which carrier testing should be performed. Yet there is very little research investigating their views on the disclosure of carrier status or the actual recommendations genetic health professionals make to parents about how to disclose carrier status or risk to their children.

This study explored genetic health professionals' views and practices around carrier testing in children by conducting in-depth interviews with 17 genetic counselors and clinical geneticists in each state and territory in Australia. This paper addresses the aspect of advice regarding disclosure of genetic carrier results to children. Interpretive content analysis was used to analyze the data.

Many of the genetic health professionals indicated that they discuss with parents both how and when disclosure might take place. However, their opinions varied about timing of disclosure of carrier status to the children, with some naming adolescence as the best time to disclose carrier status and others suggesting that earlier, later or leaving the decision to the parents might be more appropriate.

This variation in opinions and practice gives some insight into the complexity of disclosure of genetic information. This paper will suggest some explanations for this complexity, drawing on literature from other areas addressing disclosure, such as adoption and gamete donation.

Oral 2
NON-INVASIVE PRENATAL TESTING (NIPT): A NEW OPTION FOR PRENATAL TESTING

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Objective: To assess the use of Non-Invasive Prenatal Testing (NIPT) following combined Nuchal Translucency Assessment (cFTS) as a means of providing the most accurate testing for Down Syndrome (T21), Edward Syndrome (T18), Patau Syndrome (T13), and sex chromosome aneuploidy at Sydney Ultrasound for Women (SUFW). *Methods:* Patients considering further testing following cFTS were offered NIPT as an alternative to prenatal diagnosis by CVS or amniocentesis. The patient was counseled on the benefits and limitations of NIPT before testing was arranged. For those patients who did not have cFTS done with SUFW, a consult and possible scan was arranged prior to testing. NIPT was done by Verinata Health, Inc., located in the United States. The VerifyR test directly analyzes cell-free fetal DNA with our proprietary SAFeR,Ñ¢ algorithm. *Results:* There was a marked interest in this test from patients as an option for further reassurance. Patients found a benefit in having the cFTS performed as it provided them with risk information for the common aneuploidies as well as fetal wellbeing. This allowed them to make an informed decision about their best course of action. Those patients who had a positive NIPT result found that the additional information gave them the assurance that they needed to proceed with an amniocentesis. *Conclusions:* The cFTS gave patients comprehensive information on fetal wellbeing and development in addition to risk of the common aneuploidies. This provided them with the information to choose their best course of action regarding further testing.

Oral 3
NEXT-GENERATION SEQUENCING OF CONSTITUTIONAL AND GERMLINE DNA IN CLINICAL PRACTICE

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Next Generation Sequencing (NGS) is now familiar to all of us as a tool in biology, as it is to 'consumers' of genetic medicine. Consequently, we are faced with increasing expectations from patients,

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clinicians and funders alike. Yet NGS is still primarily a research tool, and it is not clear how it can best be used in a clinical or a diagnostic setting. I will discuss the work of the Translational Genomics Unit in Leeds in the United Kingdom and at the Centre for Translational Pathology in Melbourne, where we have developed translational applications of NGS in the genetics clinic and in tumor testing.

We explored several options for genetic testing in both a research and a service setting: small gene panels by PCR, large capture panels, methods for measuring gene dosage, custom amplicon kits and exome analysis. Clinical genetics testing was pursued as an incremental improvement over existing methods rather than a revolutionary change, with testing moving from single gene panels to larger sets. Annotation and databasing of the variants required progressive enhancement of data handling. As the scale of the analysis increased we had to develop a pipeline from raw data files, via alignment and annotation to database storage. Tumor testing from fixed tissue presented unique problems associated with formalin induced DNA damage, and we develop a novel approach for the analysis of low complexity targets called grouped read testing. By this method we are able to see variants at levels as low as 2% of the predominant sequence.

Oral 4
DEFINING DYSMORPHIC SYNDROMES IN THE EXOME ERA: FLOATING HARBOR SYNDROME AS A CASE EXAMPLE

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Exome sequencing has unearthed the cause of many dysmorphic syndromes and enabled phenotypic boundaries to be defined. Prior to exomes, dysmorphologists categorized most syndromes on phenotypic patterns alone. For syndromes with non-specific features and no available diagnostic test, this led to variability in how a diagnostic label was applied. Floating Harbor syndrome (FHS) is a good example. The original reported patients had short stature, speech delay and quite uniform dysmorphology. Subsequent reports broadened the phenotype to include more variable dysmorphology, leading to uncertainty about the limits of the phenotype. We previously showed that heterozygous truncating SRCAP mutations caused FHS, by exome sequencing a cohort of typically affected individuals. Subsequent testing of both facially typical and atypical patients has enabled confirmation of the key features of FHS. We present the features in more than 50 mutation-positive individuals with FHS aged from 2 to 52 years. All mutations were truncating and occurred between codons 2,407 and 2,517 in exon 34 resulting in loss of three C-terminal AT-hook motifs. We also review all previously published FHS patients where possible with SRCAP mutation testing. The cohort of 50 patients and reappraisal of published patients enables definition of the FHS phenotype and its boundaries. Of the requisite features, some variability in the severity of short stature and speech-language impairment is observed, but the facial dysmorphology and body habitus are remarkably constant. In the case of FHS, exome sequencing has enabled confirmation of quite a uniform dysmorphic syndrome caused by a restricted range of mutations within SRCAP.

Oral 5
IFT140/IFT140 MUTATIONS SHOWN TO CAUSE CAULI MOUSE AND JEUNE SYNDROME: A NEW BIOLOGIC MODEL FOR THE STUDY OF CILIOPATHIES

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Defects in cilia formation and function result in diverse ranges of human skeletal and visceral abnormalities, termed 'ciliopathies'. As part of an ENU mouse mutation screen, we identified a mutant, cauli, with a phenotype consistent with an underling ciliopathy. Mutant cauli embryos are characterized by mid-gestation lethality, craniofacial dysmorphism, neural tube defects, short, disorganized ribs, polydactyly, syndactyly, and internal organ defects. Linkage and candidate gene sequencing revealed homozygous mutations in the cilial gene, Ift140, as the cause of the cauli phenotype.

In mutant embryos; skeletal preparations revealed defects of the craniofacial skeleton, vertebrae, and thoracic rib cage; in situ hybridization with myogenin showed disordered somite patterning, and with Msx1 and Sox9 abnormalities of the axial neural tube; and examination of primary cilia showed abnormal morphology, consistent with a defect of retrograde cilial transport. Components of the Shh/Grem1/Fgf signalling systems involved in limb development were also analysed by in situ hybridisation, showing consistent disruption of expression patterns between controls and cauli mutants.

The cauli phenotype is reminiscent of human short-rib polydactylies (SRP). We screened a cohort of patients with SRP phenotypes and found a novel, homozygous IFT140 mutation in a patient diagnosed with Jeune syndrome. These data confirm the utility of this mouse model to further understand the pleiotropic anomalies that arise in Jeune syndrome and other skeletal ciliopathies. It provides a platform for further analysis of the developmental signalling systems regulated via the primary cilium.

Oral 6
PSYCHOSOCIAL IMPACT OF OFFERING CARRIER SCREENING FOR FRAGILE X SYNDROME

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Population carrier screening for FXS identifies women at increased risk of having an affected child, and provides information about their own health risk. There is debate around educational and counselling complexities inherent in such screening. Aim: to assess decision-making, knowledge and attitudes in non-pregnant and pregnant women offered FXS carrier screening.

Women are approached through general practice, obstetric or ultrasound clinics, receive written information and telephone pre-test counselling with consent. At home, women decide about testing and complete a questionnaire (Q1), mailed back with their buccal sample. Premutation (PM) or grey zone (GZ) results are discussed by telephone and women offered genetic counselling; test-negative results are mailed.

To date, 700 non-pregnant and 433 pregnant women consented; 85% and 81% returned Q1, while 71% and 61% were tested, respectively. 0.4% received a PM and 1.8% a GZ result. 85% had good knowledge (â‰¥7/10 correct). 77% non-pregnant and 68% pregnant women had positive attitudes. Pregnant women were less depressed and less stressed than non-pregnant women on the Depression Anxiety Stress Scale, with no differences between tested and non-tested. Scores on this scale were in the normal range for

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all but a few women. Decisional conflict and regret varied between groups, but were also in the normal range.

The majority of women offered screening had good understanding with minimal psychosocial impact. This may be related to pre-test counselling embedded within this study, an important element for consideration in screening programs. Overall, women supported availability of being offered screening, although testing before pregnancy is preferred.

Oral 8
PRENATAL DIAGNOSIS IN VICTORIA AND INCREASING IDENTIFICATION OF FETAL ABNORMALITIES

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Prenatal chromosome microarray testing has recently been introduced with the promise that this high-resolution technology would detect more fetal abnormalities than traditional karyotyping. Through our collection of data over the past 30 years on uptake rates of, indications for, and karyotype abnormality detection rates from prenatal diagnostic testing, we are in a unique position to show the degree to which prenatal microarray testing will impact on detection rates of fetal abnormalities.

Between 2007 and 2011, the number of prenatal diagnostic tests done in Victoria has remained around 4000, but the overall detection rate of abnormalities has gradually increased to approximately 10%. Within indication groups this figure varies. Specifically, when the diagnostic test is done because of abnormal ultrasound, the fetal abnormality detection rate is between 20-23%, is 11-12% for pregnancies with increased risk 1st trimester combined screening results and is 3-4% for women of advanced maternal age.

In 2012, at least 460 samples were analysed using chromosome microarrays, of which 86% were for a fetal abnormality on ultrasound. Within this one year period, the overall detection rate of chromosome abnormalities has risen to 12%. As microarray testing is used more frequently to analyse fetal samples for women undergoing diagnostic testing for other clinical indications (e.g., abnormal first trimester combined screening and advanced maternal age), further increases can be expected. Ongoing monitoring of trends in prenatal testing is therefore important to inform counselling practice, and to anticipate potential changes in prenatal and perinatal health service needs and adequately prepare for them.

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