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Medical Genetics Conference Kuala Lumpur 2022: The Future is Now: Challenges and Innovative Solutions in Genetic Diagnostics, co-organised by Medical Genetics Society of Malaysia, Chapter of Medical Genetic Pathology, College of Pathologists, Academy of Medicine of Malaysia and Pantai Premier Pathology and held on 7th – 9th September 2022. Abstracts of plenary, talk, symposium and paper (oral and poster) presented are as follows:

Plenary I: Genetic investigation of the child with intellectual disability

David Amor

Lorenzo and Pamela Galli Chair, Department of Paediatrics, The University of Melbourne Australia

The search for causation is a key component of the assessment of the child with intellectual disability. Historically, a specific diagnosis was achievable in only a minority of these children, but over the last decade, this has changed dramatically such that a specific diagnosis is possible in about half of all children with intellectual disability. This improvement has been driven by advances in genetic-testing technologies, most importantly chromosome microarray and whole exome sequencing. Simultaneously, these technological advances have revealed many new genetic syndromes that had previously escaped clinical recognition, and demonstrated that the majority of severe intellectual disability is caused by pathogenic gene variants that arise de novo in the child. Evidence from health economic studies suggests that this testing is most cost effective when performed early in the patient's diagnostic journey. The next challenge is to harness new research technologies to diagnose previously unsolved cases.

Plenary II: Lung cancer: The poster child for personalised medicine in oncology

Liam Chong Kin

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In recent years, lung cancer has moved to the forefront of the 2 most important trends in medical oncology - namely, targeted therapy and immunotherapy. The personalised medicine treatment landscape for advanced non-small cell lung cancer (NSCLC) patients has been evolving at an impressive pace, with many targeted therapies approved. Current guidelines recommend predictive biomarker testing before initiating first-line therapy in patients with advanced non-squamous NSCLC. The activating genetic alterations to be tested have expanded beyond *EGFR*, *ALK* and *ROS1* to include $BRAF^{V600E}$, *MET, RET*, *NTRK*, $KRAS^{G12C}$, *EGFR exon 20 insertion and HER2*. Exclusionary testing, involving upfront testing for *EGFR* and *ALK* followed by targeted next-generation sequencing for the other less common actionable genomic alterations is the most efficient and cost-saving strategy. For advanced squamous NSCLC, molecular testing should be considered in patients who are never-smokers, those with mixed histology or small biopsy specimens. A reflex molecular test standing order allows molecular testing on confirmation of a NSCLC histology resulting in a short turnaround time, avoiding the need for individual test requests and to conserve tissue. Although an imperfect predictive biomarker, tumour PD-L1 expression is used to select immune checkpoint inhibitors (ICIs) as a monotherapy or in combination with chemotherapy or with another ICI in NSCLC patients without targetable oncogenic drivers. More recently, adjuvant therapy with osimertinib in completely resected stage IB-IIIA *EGFR*-mutant NSCLC and with atezolizumab following adjuvant chemotherapy in completely resected stage II-IIIA NSCLC with PD-L1 expression of ≥1% has been shown to improve disease-free survival.

Plenary III: Technological changes in prenatal screening and diagnosis: From chromosomes to genomics

Mark Pertile[1,2,3]

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The past two decades has seen rapid advances in prenatal diagnosis and screening, as technologies have taken full advantage of the completion of the human genome project. Prenatal diagnosis of chromosome and single gene conditions has evolved from light microscopy and targeted PCR techniques to chromosome microarray (CMA), sequencing-based copy number detection (CNV-Seq), targeted gene panels, and whole exome and whole genome sequencing (WES, WGS), with newer technologies like optical genome mapping (OGM) on the horizon. Next generation sequencing of cell-free DNA in maternal plasma has also led to a reduction in the number of prenatal diagnostic procedures, which have fallen dramatically due to the superior screening accuracy of NIPT. Despite this rapid decline in procedures, the number of clinically significant genetic conditions identified during pregnancy are at historic highs.

TALK

Fetal, Maternal & Reproductive Genomics

The role of pre-implantation genetic testing (PGT) in fertility management

Zainul Rashid Bin Mohamad Razi

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Since the introduction of Prenatal Genetic Diagnosis (PGD) into our Fertility Practice by Verlinsky & Kuliev in 1996, this procedure has been practised by leaps and bounds by many fertility centres more than a decade later. The change of name from PGD to Preimplantation Genetic Screening (PGS) and finally Preimplantation Genetic Testing (PGT) just showed how dynamic this new technology has evolved over a short period of time. Unfortunately, this new technology has not undergone the vigorous tests regarding its safety and efficacy with appropriate validation studies before its introduction into clinical practice. PGT is introduced into the ART fraternity to improve the pregnancy rates, reduce the miscarriage rates and shorten the duration to conception upon starting fertility treatment. However, meta-analyses performed on most of the earlier ART cases following PGT had not shown these improvements. This is because PGT is currently performed on almost all patients going for ART by many fertility centres due to its monetary gain. Using PGT in ART on targeted patients who are elderly or have low ovarian reserve will further reduce the number of embryos available for transfer resulting in reduced pregnancy rates. Despite earlier assumptions, a single Trophectoderm Biopsy (TEB) cannot provide reliable information about the chromosomal constituency of the whole Trophectoderm. Moreover, the trophectoderm does not reflect the Inner Cell Mass (ICM) because the ICM will eventually forms the embryo while the trophectoderm develop into the placenta. Lastly, it has been shown that embryos can actually "self-correct" aneuploidy and mosaicism downstream at blastocyst stage. PGT definitely has a role in ART. However, it should be performed on selected cases such as those with recurrent IVF failures, recurrent miscarriages and known genetic/ chromosomal anomalies in previous babies or in either/both parents.

Advantages and limitations of a genome-wide approach to NIPT

Mark Pertile[1,2,3]

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Many centres around the world now offer cell-free DNA screening of pregnancy in a genome-wide capacity. The main advantage of genome-wide non-invasive prenatal testing (NIPT) is the opportunity to identify chromosome conditions beyond the common trisomies. Additional findings include rare autosomal aneuploidies, copy number variants from 7-10 Mb in size (primarily duplications and deletions), and more complex structural chromosome abnormalities including isochromosomes and unbalanced translocations. Against these additional findings is an increase in the false-positive rate, often caused by biological phenomena such as maternal constitutional mosaicism, maternal acquired abnormalities (both malignant and benign), placental mosaicism, and co-twin demise. This presentation draws on local and global experience to highlight the advantages and limitations of a genome-wide approach to NIPT.

Gender dysphoria and disorders/ differences in sex development (DSD)

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Gender dysphoria (GD), also known as Gender Identity Disorder (GID), refers to the condition where individuals experience conflict between their gender identity and their assigned gender, resulting in significant distress and impairment. Disorders / Differences of Sex Development (DSD) refers to a congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical. DSDs are classified into three categories based on their karyotypes, where each category consists of several different diagnoses. One of the most difficult issues in managing a child with DSD diagnosis, especially in cases of ambiguous genitalia, is the assignment to the more appropriate gender and from a parent's perspective, the gender of rearing. The primary goal in DSD is for gender identity to be consistent with the gender assigned and to avoid a gender assignment that would increase the risk of gender dysphoria (GD). The overall prevalence of GD in DSD is 15%. Some diagnoses such as those with 46,XY karyotypes but born with female external genitalia such as 5-alpha reductase deficiency and 17- beta hydroxysteroid dehydrogenase 3 deficiency have gender dysphoria rates as high as 53%. Whereas, other patients with 46,XY karyotypes such as the diagnosis of Complete Androgen Insensitivity Syndrome (CAIS) brought up as female retain their female gender identity and do not experience GD. A small minority of DSDs may feel the need to change gender in life, thus the assigned gender should not be considered immutable. A multidisciplinary team is recommended to manage such cases.

Genetic counselling in genomic medicine: New challenges and opportunities

Thong Meow-Keong

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Genomic medicine is defined as ''an emerging medical discipline that involves using genomic information about an individual as part of their clinical care and the health outcomes and policy implications of that clinical use'' (National Human Genome Research Institute [NHGRI]). While the main focus is on these exciting new frontiers, there is an urgent need to address the issue of delivery of genomic medicine towards the healthcare of the population. There are genuine concerns that advances in genomic medicine will create an acute shortage of qualified genetic professionals with competency to practise safely in this field. In addition, some medical practitioners advocated that with the use of genomic technology, genomic testing should be available as a part of 'routine' patient testing repertoire. This lack of understanding of genomics in healthcare raised the question on the role of genetic and genomic counselling provided by medical practitioners and the steps needed to overcome these challenges. Typically, genetic counsellors work with clinical geneticists and clinical scientists with the focus on providing information, interpreting genetic information to patients and to provide support and care for the patients and their families. In recent years, the scope of genetic counselling expanded to include interpreting variants, arranging complex genomic testing, assessing patients for appropriate disease screening and handle all the consequent psychosocial and ethical issues raised. Many have also taken on tasks which evolved into research, policy, education and more recently mainstreaming the genomic advances. Hence, the term 'genomic counselling' was advocated.

Genetics in the obstetric clinic: An obstetrician's view

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One of the most important roles of an obstetrician is to assess the fetal wellbeing in a pregnancy. On the average fetal abnormalities will be identified in about 2-5% of pregnancies. This is traditional associated with fetal structural defects. This is done by performing an antenatal scan. Ultrasound has increasingly established itself as the primary imaging tool is obstetrics. In recent years, the improvement in ultrasound technology has increased our ability to identify fetal abnormalities at increasingly earlier gestations. But structural defects are only one half of the story; the other half is provided by genetic abnormalities. For many years the primary diagnostic test was confined to fetal karyotyping by G-Banding technique and a handful single gene disorders and inborn errors of metabolism. In the last 10-12 years there has been a massive disruption in the field of genetic testing The spectrum of tests has increased, due to rapid development newer laboratory techniques and procedures. And these tests are being provided at affordable cost. Due to the availability of increase choices in genetic screening and diagnostic tests; there is a need for obstetricians to keep themselves updated. In depth knowledge of clinical genetic tests including the scope of testing and turnaround time of tests will allow the doctor offer appropriate tests for right patient to optimize fetal outcomes. Increased pick up rates of fetal abnormalities during an antenatal scan demands testing for a wider range of genetic conditions. The time has come for the obstetricians to recognise fetal genetics in a pregnancy is beyond testing for Trisomy 21. As such, provision of comprehensive testing to ensure the genetic wellbeing of the developing fetus is now expected in an obstetric clinic. Needless to say, with increasing availability of detailed information in public domain; the patient is often well informed. It is hoped that their doctors are better informed!

Rare diseases

Ngu Lock Hock

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In Malaysia, rare disease is defined as a life-threatening and/or chronically debilitating rare condition as listed in the Malaysian Rare Disease List. The criteria for inclusion a disease in the Malaysian Rare Disease List are: (a) There are confirmed patients in Malaysia; (b) The disease affects fewer than 1 in 4,000 people in Malaysia; (c) The disease is a severe condition; (d) Its inclusion is approved by the Ministry of Health's National Rare Disease Committee. Although individually uncommon, rare diseases are common in the aggregate. The large majority of these diseases has a genetic origin. Management of rare diseases is largely facilitated through clinical geneticists in collaboration with other medical disciplines. Rare diseases pose particular challenges to patients who are affected, to the clinicians who care for them, and to the researchers who study their conditions. The challenges to patients with a rare disease are threefold: they may experience the manifestations of the disease but struggle to find doctors knowledgeable about their condition to manage them; they may suffer the consequences of the disease and go completely unrecognised; and they may be faced with very high costs for disease-specific medications. Generally, the awareness level among Malaysian doctors about rare diseases is still low compared to their familiarity with other conditions. Although Malaysia has made significant progress in the management of rare diseases, but there are still opportunities for development in critical areas. All stakeholders: healthcare providers, government, society, and politicians need to work together to improve the management of rare diseases in our country.

Genetics of childhood epilepsy – more questions than answers?

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Advances in genetic testing has dramatically improved the ability to unveil genetic aetiologies to diseases across many disciplines. For childhood epilepsy, where traditionally a syndromic approach is commonly used, an increasing number of genetic variations are being recognised in association with specific epilepsy syndromes. Getting a genetic diagnosis helps to choose appropriate investigation and treatment and allows for more accurate prognostication and counselling of families. For example, finding a mutation that blocks the functioning of sodium channels in an infant with severe epilepsy will obviate the need for neuroimaging, caution against the use of sodium channel blockers such as carbamazepine and guide estimates of recurrence risks. However, determining pathogenicity of a given variant can be challenging, therapies targeting at functional disturbance do not always work and phenotypic variability complicates prediction of outcomes and recurrence. In this talk, I will give examples of how genetic diagnosis impacted patient care, and the difficulties that we face in this era of new genetics.

The Role of WHO and UNESCO in the development of medical genetics in LMIC

Zilfalil Bin Alwi

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Advances in genetics and genomics technology have rapidly changed health-care services throughout the world. However, the application of cutting edge genomics in medical genetics is nascent in many low- and middle-income countries (LMIC). As a result, many of LMICs have varying capacities for performing and interpreting medical genetics methods such as PCR, Array CGH and DNA sequencing. This situation has put them in a disadvantaged position and made them less likely to be included in international genomic initiatives. Recently, the World Health Organisation (WHO) Science Council advocated recommendations on accelerating access to genomic for global health to aid the LMIC in addressing the obstacles in medical genetics. UNESCO supports medical genetics through the establishment of Human Variome Project (HVP) by establishing a global-wide initiative, Global Globin Network (GGN), which aims at addressing the genomic divide among the LMIC. Although there are many impediments to the implementation of cutting edge genomic methods in LMICs, the application of genomic technologies are crucial for improving the health and livelihood of people in all parts of the world regardless of economic status.

CANCER - PERSONALISED MEDICINE

Precision medicine: An update

Roziana Ariffin

Pantai Premier Pathology, Malaysia

Precision medicine is a bold new approach, in revolutionising how we improve health and treat disease. Until now, most medical treatments have been designed for the "average patient." As a result of this "one-size-fits-all" approach, treatments can be very successful for some patients but not for others. Precision Medicine, on the other hand, is an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles. It gives medical professionals the resources they need to target the specific treatments of the illnesses we encounter, further develops our scientific and medical research, and keeps our families healthier. The future of precision medicine will enable health care providers to tailor treatment and prevention strategies to people's unique characteristics, including their genome sequence, health history, lifestyle, diet even their microbiome composition. To get there, we need to incorporate many different types of data, from metabolomics (the chemicals in the body at a certain point in time), the whole genome and sometimes even the microbiome (the collection of microorganisms in or on the body), and data about the patient collected by health care providers and the patients themselves. Success will require that health data is portable, that it can be easily shared between providers, researchers, and most importantly, patients and research participants. This lecture will address precision medicine in breast, lung, colorectal cancer and melanomas as some examples. This list is by no way exhaustive and is increasing by day. Advances in precision medicine had now led to powerful new discoveries and several new treatments, that improved chances of survival and reduce exposure to adverse effects.

Molecular characterisation of non-Hodgkin lymphoma

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Non-Hodgkin lymphomas evolve from the clonal expansion of mature B, T and natural killer (NK) cells in different stages of development. Scientific efforts have been undertaken to identify and understand the molecular changes associated with the malignant transformation of these lymphoid cells. B cells undergo two late changes to the DNA during the germinal centre reaction i.e., hypermutation and class switch of the immunoglobulin heavy chain gene for immune system diversity. This heterogeneity might trigger alterations which may lead to lymphomagenesis. A broad number of genetic alterations, such as chromosomal translocations and alterations, somatic mutations and epigenetic alterations, are also seen in virtually all lymphoma subtypes. Many of these genetic changes are now incorporated into the WHO's defined criteria for diagnostic evaluation of lymphoid neoplasms. They also have implications in risk stratification, prognosis and disease monitoring and used for targeted treatment of lymphomas.

The genes, the molecules and therapeutic implication in triple negative breast cancer

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The choice of treatment for breast cancer can be personalised based on the cancer type, stage, and genetics. Triple-negative breast cancers (TNBC) are breast cancers that lack expression of the Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Receptor 2 (HER2) gene amplification. Intensive analysis by the Cancer Genome Atlas (TCGA) Research Network and the advent of high-throughput technology tools have expanded the classification of TNBC tumours into subgroups according to its gene expression profiles, novel TNBC biomarkers and germline testing for hereditary predisposition can play both predictive and prognostic roles. Hereditary breast cancers are different from sporadic cancers and genetic test results may influence or enhance therapeutic strategies. The "immune-activated," subtype or tumours with defective BRCA pathway are amongst initial TNBC group with established genetic vulnerabilities that has allowed the addition of promising therapeutic approaches, including DNA-damaging agents (PARP inhibitors, platinum) as well as immunotherapy. The treatment of metastatic NBC (mTNBC) is currently transforming rapidly with better outcomes observed in clinical trials. The recent success with immune checkpoint inhibitors (ICIs) targeting the programmed cell death receptor 1 and programmed death ligand 1 (PD-L1) and PARP inhibitors for germline BRCA mutation-associated breast cancers as well as other novel strategies in mTNBC treatment will change the course of this unique cancer subtype in the future.

Genetic & genomic landscape of prostate cancer

Lim Chun Sen

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Over the last decade, genomic profiling has become a very important test to guide therapeutic approaches in most of cancer. Hence, understanding the genomic profiling of prostate cancer is crucial, owing to the emergency of precision medicine to guide for right treatment. There are now several FDA approved biomarkers and commercially available clinical laboratory improvement amendments-based tests to help guide clinicians and patients in deciding whether or not biopsy screening is necessary. A number of metastatic prostate cancer harbour clinically actionable molecular alterations, including DNA damage repair (e.g., *BRCA*1/*2* and *ATM*) and *PTEN*/phosphoinositide 3-kinase signaling. Heterogeneity of the genomic landscape of metastatic castration resistant prostate cancer is more prevalence, approximately 25% carry an HRR mutation. In Malaysia, the prevalence of BRCA1/2 mutation is reported 12% among metastatic prostate cancer patient. There are treatment options for metastatic prostate cancer patients in different stages of presentation that harbours *BRCA*1/2 or *ATM* mutation. Besides, genomic alterations of *TP53*, *RB1*, *AR*, and cell cycle pathway are associated with poor clinical outcomes in patients.

Current perspective and the future of liquid biopsy

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Liquid biopsy has revolutionised the field of clinical oncology, and it is just at its infancy. The information collected from circulating tumour cells (CTCs) and cell-free DNA (cfDNA) opened up opportunity to prognosticate patients without the agony of invasive procedures. It is rapidly establishing itself as a feasible diagnostic alternative and in selected cases drives treatment decisions. However this technology comes with limitations, which is why most of the discoveries have yet to be available in routine clinical practice. Research opportunities are immense and such research will help shape the future of oncology.

How to overcome financial toxicity of lung cancer treatment?

How Soon Hin

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Lung cancer is the most common cause of cancer-related death in Malaysia, accounting for almost 20% of all cancer deaths in the country. The vast majority of lung cancer patients in Malaysia present in late stages of the disease, whereby 90% are diagnosed in stages Ill or IV at presentation. Overall survival of advanced stage non-small cell lung cancer (NSCLC) had been improved by targeted therapy and immune check point inhibitor (ICI). However, there are challenges in making these therapies universally available in a resource limited setting. Modification of the regime may be useful to overcome financial toxicity, in addition to seeking various funding and enrolling patients into clinical trial or compassionate programme.

Colorectal cancer: Update in the era of personalised medicine

Matin Mellor Abdullah

Subang Jaya Medical Centre, Malaysia

Colorectal cancer is a common cancer and 2nd most common cause of cancer mortality worldwide. Up to 20% present with systemic spread, while those who present with loco-regional disease, up to 50% will eventually develop metastatic disease. Only a small percentage of cases with stage 4 disease are curable by currently available treatment thus constitutes a significant public health challenge due to morbidity, mortality and cost of treatment. For a very long time the mainstay of colorectal cancer treatment was systemic chemotherapy irrespective of location. With advancement in molecular pathology, a plethora of mutations have been identified making colorectal cancer a heterogeneous disease with many molecular alterations, altering of the signaling pathways causing tumour onset, progression and metastases. Some of these alterations are amenable to targeted therapy with an improvement in the disease free and overall survival. Colorectal cancers are being stratified based on their molecular alterations and current treatment algorithm takes that into account. The next step will be to integrate the knowledge of genetic alteration, tumour microenvironment, protein expression profiling, host immune competence as well as changes at different phases of the disease continuum to fully realize the promise of precision/personalise treatment. This may identify predictive and prognostic markers that may inform the treating physician of the most appropriate treatment.

Multiple myeloma

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Multiple myeloma (MM) is an uncontrolled proliferation of monoclonal plasma cell of antibody-secreting plasma cells (PC) in the bone marrow (BM) that is often diagnosed by the presence of a typical M-spike by serum protein electrophoresis (SPEP) or by free light chains in the urine. The cell of origin is a B-lymphocyte acquiring aberrant genomic events in the germinal centre of a lymph node as off-target events during somatic hypermutation and class-switch recombination driven by activation-induced-deaminase. The pathogenesis is due to the dysregulated expression of a cyclin D gene, either directly by juxtaposition to an immunoglobulin enhancer, as a result of ectopic expression of a MAF family transcription factor, or indirectly by as yet unidentified mechanisms. It is divided into two distinct genetic subtypes based on chromosome content. Hyperdiploid myeloma is characterized by multiple trisomies of chromosomes 3, 5, 7, 9 11, 15, 19 and 21, and lacks recurrent immunoglobulin gene translocations. Non-hyperdiploid myeloma in contrast is characterized by chromosome translocations t(4;14), t(14;16), t(14;20), t(6;14) and t(11;14). There may be secondary genetic events include rearrangements of MYC, activating mutations of NRAS, KRAS or BRAF, a promiscuous array of mutations that activate NFkB and deletions of 17p. Among the poor-risk genetic features are t(4;14), t(14;16), t(14;20), del 17p and gains of 1q. Available evidence supports the use of a risk-stratified approach to the treatment of patients with multiple myeloma, with the early and prolonged use of bortezomib particularly in patients with t(4;14) and del 17p. A better understanding of the molecular pathogenesis of myeloma progression would allow stratification of patients based on their risk of progression, thus rationalising efficacy and cost of clinical interventions.

PARP inhibition as frontline therapy in ovarian cancer

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In Malaysia, ovarian cancer ranked second most common gynaecological cancer after cervical cancer with age-standardised rate (ASR) of 5.9 per 100,000 (Malaysian National Cancer Registry 2007). Ovarian cancer remains a challenging gynaecological cancer to manage and the mainstay of treatment for ovarian cancer is still surgery and chemotherapy. It has been an exciting time now with new evidences emerging on the management of ovarian cancer with introduction of new therapies. PARP inhibitors

are an exciting new treatment option for patients with ovarian cancer and targeting defective DNA damage repair using PARP inhibitors has demonstrated excellent improvements in ovarian cancer therapy. Multiple phase III trials continue to advance the role of PARP inhibitors in ovarian cancer, most prominently SOLO1 (frontline olaparib), PRIMA (niraparib in higher-risk patients), PAOLA-1 (olaparib plus bevacizumab), and VELIA (veliparib plus chemotherapy). Each trial met its primary end-point of progression-free survival (PFS), and subsequently olaparib, niraparib, and olaparib/bevacizumab all were approved as frontline maintenance therapy in ovarian cancer by the FDA and European Medicines Agency (EMA).

NEW TRENDS IN TRANSLATIONAL GENOMICS

Is genomics the future of newborn screening?

David Amor

Lorenzo and Pamela Galli Chair, Department of Paediatrics, The University of Melbourne Australia

Genomic newborn screening (gNBS) brings the potential to optimise the health and well-being of children and families, however screening programs are required to be evidence based, acceptable, and beneficial. Although discussions about gNBS to date have been largely hypothetical, evidence is starting to emerge from the first gNBS pilot projects, addressing the following questions: (1) what is the interest in and what would be the uptake of gNBS? (2) what diseases and genes should be included? (3) what is the validity and utility of gNBS? and (4) what are the ethical, legal, and social implications? This evidence highlights the importance of equitable access, appropriate educational materials, and informed and flexible consent. Selecting genes for testing is critical, and reflect that parents value the certainty of prediction over actionability, and data should be analysed in a way that minimizes uncertainty and incidental findings. The expansion of traditional newborn screening (tNBS) to identify more life-threatening and treatable diseases needs to be balanced against the complexity of consenting parents of newborns for genomic testing as well as the risk that overall uptake of tNBS may decline. Overall, implementing gNBS will require a nuanced approach, including consideration of the views of diverse populations, the capabilities of health systems, and health economic implications. It will be essential to rigorously evaluate outcomes and ensure programs can evolve to maximise benefit.

Genetic testing of inherited endocrine disorder

Dr Roziana Ariffin

Pantai Premier Pathology, Malaysia

Genetic testing in a diagnostic workup of inherited endocrine disorder depends on the appropriateness to accurately detect disease causing and modifying mutation, their informational value and cause effectiveness. Early diagnosis of genetically based endocrine disorder enables precise accurate management and help patients and their families not only with well-informed choices to navigate their lives but to accurately assess prognosis, recurrent risk, family planning, and genetic counseling. Asymptomatic carrier of pathogenic variant can be identified, and prenatal testing can be offered where appropriate. With Next Generation Sequencing, the knowledge of the aetiology of inherited endocrine disorder has massively expanded, however with this new molecular tool, interpretation of diagnostic data, is becoming increasingly complex. This lecture address, the classical mode and some not classical mode of inheritance in inherited endocrine disorder. Methods, target region, chances/advantages, limitation and disadvantage of various methods are discussed. Example of some disorders are highlighted, and the importance of incorporation of many types of data, from metabolomic, clinical exome, whole exome, whole genome and methylome among others will be addressed.

Molecular profiling for precision medicine in heritable cancer: When somatic tumour testing and germline mutations meet and the way forward

Firoz Ahmad

Molecular Pathology and Lab Operations-Genomics, SRL Ltd, Mumbai, India

About 5%-10% of cancers are hereditary in nature and certain genetic variants that are often inherited from a parent increase the risk of developing a particular type of cancer. Clinical genetic testing for cancer-risk assessment has become widespread over the last few years, with evidence-based testing guidelines for hereditary breast and ovarian cancer. For example, presence of BRCA1 and BRCA2 mutation in individuals with a strong family history of cancer, there is a 50-80% increased risk of developing breast cancer and or 40-60% of ovarian cancer by the age of 70. Similarly, mutation in APC gene increases the risk for developing colon cancer, CDH1 mutation increases risk of hereditary diffuse gastric cancer, SMAD4 mutation for prostate cancer so on and so forth. These genomic variations can be easily screened by single gene or multiple genes testing simultaneously by the help of NGS technology. Personalised medicine involves using information about a person's cancer to help diagnose, treat and find out about how well treatment is working. It is interesting to note that identification of predictive and actionable mutations in the homologous recombination repair (HRR) pathway has gained tremendous attention in recent time. The approval of PARPi has led to guideline bodies such as the National Comprehensive Cancer Network (NCCN) to

actively recommend germline and or somatic HRR gene panel testing to identify patients who will benefit from PARPi in metastatic castration-resistant prostate cancer and also in Ovarian and breast tumours. More interestingly, molecular profiling of Homologous recombination deficiency (HRD) in ovarian cancer has proven to be a milestone precision oncology test which allows deciding PARPi treatment in advanced disease. In the absence of a germline or somatic BRCA1/2 mutation, homologous recombination status may provide information on the magnitude of benefit of PARP inhibitor therapy. Thus, comprehensive genomic cancer profiling enables personalised cancer treatment and aids in germline findings.

Prenatal screening & diagnosis of thalassaemia

Carol Lim Kar Koong

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Thalassaemia is the commonest genetic condition globally, affecting around 5-7% of the world population. In Malaysia, the prevalence of thalassaemia is close to global rate, with a recent publication reported 6.8% prevalence rate from the 2007-2018 data of Malaysian Thalassaemia Registry. The highest number of patients were from the state of Sabah (23.03%). Being the referral centre for adult thalassaemia patients, Ampang Hospital serves the highest number of patients (703, 8.81%), followed closely by Queen Elizabeth Hospital (370, 4.63%) and Sabah Women & Children Hospital (300, 3.76%), both based in Kota Kinabalu, Sabah. The Malaysia Ministry of Health has introduced Thalassaemia Prevention and Control Program in 2004 and school thalassaemia screening program in 2016, involving Form 4 students. Various prenatal diagnostic modalities have been available for many years, with most of the laboratory service currently provided by private sectors. Less invasive technique such as cell-free fetal DNA in prenatal diagnosis would be more acceptable to many patients. However, with the majority of the laboratory service catered by the private labs, it has invariably made it less accessible or affordable to most patients. This certainly is the case for cffDNA & preimplantation genetic testing (PGD). High cost is one factor that prenatal diagnosis among the pregnant thalassaemia patients is not well taken up and the number of thalassaemia births did not drop significantly. Nevertheless, non-invasive technique is the way-forward in providing prenatal diagnosis for affected couples, with minimal risk to the mothers.

SYMPOSIUM

Symposium I: The application of chromosomal microarray technology in reproductive health research

Michael Richardson

Reproductive Health, Thermo Fisher Scientific, Singapore

In recent years, reproductive health research has witnessed a significant transition from traditional non-molecular techniques to molecular genetic based technologies. These new molecular methods provide for simpler, faster tests, yield increased information and, in some cases, are less invasive. Molecular technologies are being applied at different stages of the reproductive cycle, providing research solutions across the entire journey, including preconception carrier screening, preimplantation genetic testing, pre and post-natal testing, and newborn screening. In prenatal research, chromosomal microarrays are now routinely used to examine samples from invasive procedures such as amniocentesis and play a vital role in providing information about the health of the fetus. In postnatal research, microarray technology has been the recommended first tier test for developmental disabilities and congenital anomalies since 2010. Recent research has also emphasized the importance of single exon copy number variations in understanding genetic mutations in unresolved postnatal testing cases. In both pre- and post-natal research, the application of these technologies enables a comprehensive analysis to aid understanding of genetic disorders. In this talk, I will provide an overview of microarray technology and will discuss how Thermo Fisher Scientific chromosomal microarray technology can be applied in applications of pre- and post-natal research.

Symposium II: Six years' experience of a non-invasive prenatal testing (NIPT) laboratory in Singapore

Sherry Ho

iGene Laboratory Pte Ltd, Singapore

Noninvasive Prenatal Testing (NIPT) reduces the need for invasive procedures. Over a 6-year period from 1 January 2016 to 31 December 2021, 18421 samples were processed in iGene laboratory. We evaluate the performance of NIPT in singleton and twin pregnancies. Blood samples (n=18421, singletons, 18224, twins, 197) were collected for sample processing. Reasons for referral include high risk first trimester combined screening, advanced maternal age >35 years, family history, or ultrasound abnormalities. cfDNA was extracted from maternal plasma for library construction and massively parallel sequencing, followed by data analysis using proprietary algorithm. Of the 18224 singletons, 444 (2.4%) required a blood recollection due to high data noise and low FF (<3.5%). Of the remaining 17780 samples, 226 were screened positive. Forty-six of these cases had confirmatory results with 34 true positives and 12 false positives. Of the 444 samples which require a blood recollection, 371 received a result where 16 were positive. There were 73 inconclusive results (0.4%). Of the 197 twin pregnancy samples, 276

samples were negative while 20 required a blood recollection (10.2%) with 2.5% inconclusive rate. Mean FF showed a positive correlation with gestational weeks i.e. 10.2% at ≤12.6 weeks and 13.8% at ≥25 weeks. In this study, we observed overall 100.0% sensitivity (95% CI, 85.8–100.0) and 99.9% specificity (95% CI, 99.9–100.0) for the three common trisomies, and overall 100.0% sensitivity (95% CI, 31.0–100.0) and 99.9% specificity (95% CI, 99.9–99.9) for sex chromosome aneuploidies in singleton pregnancies.

Symposium III: Next level comprehensive genomic profiling with gold-standard homologous recombination deficiency (HRD) insights

Chonglei Bi

SEA, Illumina Asia Pacific Japan

Comprehensive Genomic Profiling (CGP) uses NGS technology to assess hundreds of genes for relevant cancer biomarkers, as established in guidelines and clinical trials, to guide therapy selection. HRD is a genomic signature that can be included with CGP testing, or as a stand-alone test. As our understanding of HRD expands beyond causal genes like BRCA1 and BRCA2, many other genes may affect the HRR pathway and could be included in a CGP test. CGP also has the power to identify rare mutations and other relevant genomic signatures in ovarian, breast, prostate, and pancreatic cancers such as tumor mutational burden (TMB) and microsatellite instability (MSI). In this session, we will provide an introduction to HRD, the different components involved in evaluating this composite signature, and the benefits of including HRD with CGP testing.

Symposium IV: Molecular tumour board discussion - a patient with non-small cell lung cancer

Raja Thirumalairaj

Apollo Hospitals, Chennai, India

This case is of a patient diagnosed with metastatic lung cancer who was EGFR, ALK and ROS1 negative with hotspot RT-PCR. The NGS picked up an exon 20 insertion and showed response to afatinib. An evolution of T790m was seen after afatinib use with a liquid biopsy NGS. Inframe insertions of three or more base pairs in exon 20 of the epidermal growth factor receptor (EGFR) gene were among the first EGFR mutations to be identified as oncogenic drivers in non-small cell lung cancer (NSCLC). However, unlike the classical EGRR L858R point mutations or exon 19 deletions, which represent the majority of EGFR mutations in NSCLC, low frequency EGFR exon 20 insertions are associated with de novo resistance to targeted EGFR inhibitors and correlate with poor patient prognosis. The T790M substitution in exon 20, is thought to account for more than half of all cases of acquired resistance to first-generation EGFR inhibitors in NSCLC. It was initially predicted that the mechanism of resistance underlying the T790M mutation was steric hindrance imposed by the presence of a bulky methionine residue that would prevent the binding of first-generation EGFR inhibitors to EGFR. However, while T790M mutation was found to impact the affinity of the mutant EGFR receptor to gefitinib, inhibitor binding was not completely abolished. Crucially, further analysis revealed another major factor that contributed to drug resistance: the T790M mutation restored the ATP-binding affinity of the L858R mutant EGFR to almost wild-type receptor levels. By increasing the ATP affinity, the T790M mutation diminishes the efficacy of reversible ATP-competitive inhibitors gefitinib and erlotinib, and removes the selectivity that these drugs have for mutant over wild-type EGFR.

Symposium V: The precise decisions – unlock the potential of NGS and bioinformatics analysis in personalised medicine

Kathryn Bungartz

QIAGEN Germany

Next Generation Sequencing (NGS) provides a powerful means to identify variants involved in disease and tumourigenesis, including variants that can predict sensitivity or resistance to targeted therapies and those that ascribe prognostic or diagnostic significance. However, comprehensive genomic sequencing produces thousands of variants for cancer diagnostics, that can create bottlenecks for accurate interpretation. This is where QIAGEN Digital Insights (QDI) can help. Using augmented molecular intelligence, QDI tools, including QIAGEN Clinical Insights Secondary and QCI Interpret One (QCI) provide secondary analysis and clinical decision support software that assist molecular pathologists in the identification and classification of oncology-relevant variants. The QIAGEN Knowledgebase has been constantly growing for 20+ years, curated by our team of 200+ PhD scientists, engineers, and ontologists. The manual curation is augmented by machine learning and AI to create a source of molecular knowledge. Layered on top of QIAGEN Knowledgebase is a suite of bioinformatic tools that provide an interface to this data, including QCI. QCI Interpret One can help rapidly identify targetable alterations from large datasets derived from comprehensive panels, such as QIAseq PanCancer, TSO500, or whole exome/genome sequencing. It provides evidence-based variant prioritisation and classification. Supported by a unique blend of expert curation and automation, QCI can help the user rapidly progress from a VCF to a customisable draft report that includes on- and off-label therapies as well as clinical trials. The methodology is entirely evidence-based and transparent, providing easy traceability back to the source material, enabling the user to confidently meet clinically relevant turnaround times.

ABSTRACT

GEN01 A rare case of constitutional interstitial 5q deletion

Yi-Ting Cheng[1], Fatimah Azman[1], Roshaidie Abdul Rashid[1], Eva Foong[1], Hashima Hashim[1], Shi Yie Wong[2], Kian Ruey Saw[2], Loi Khim Chin[1]

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Introduction: Constitutional interstitial deletion of 5q region are rare, with less than 50 reported since the first in 1978. The size of the deleted regions are variable, and cytogenetic characterisation of the breakpoints are difficult. As far as we know, this is the first case of constitutional interstitial 5q deletion reported in Malaysia. *Case report:* The patient was born at term via Caesarean section for foetal distress. Dysmorphic facial features were noted with widened anterior fontanelle, single palmar crease over right palm, wide sandal gap, low set ears, and hypotelorism. Ultrasonography of the cranium shows prominent/mildly dilated temporal horns and fourth ventricle. Cytogenetic analysis revealed an interstitial deletion at 5q14-q22. *Discussion:* Interstitial deletion of the middle segment of 5q are poorly characterised, and the paucity of cases and variable presentation presents a challenge for exact genotype-phenotype correlation. Patients typically present with mental retardation and dysmorphic facial features, though the severity of mental retardation and extent of deletion is not well-correlated. There are many genes of interest in this region, among which deletion of *MEF2C* and/or *APC* genes may result in a gene deletion syndrome with far-reaching consequences. *MEF2C* haploinsufficiency presents with intellectual disability, developmental delay, lack of speech, and seizures, and has also been implicated in autism. Whole gene deletion of *APC* gene can cause familial adenosis polyposis (FAP). Thus, molecular characterisation of the deletion is important to determine the genes deleted, and if any gene deletion syndromes are associated with it.

GEN02 Molecular diagnosis of myotonic dystrophy type 1 (DM1) in Malaysian patients

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Introduction: Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystem disorder that is primarily characterised by myotonia and progressive muscle weakness. It is caused by unstable CTG microsatellite expansion in the 3' untranslated region (UTR) of the *DMPK* gene. *Materials & Methods:* We received whole blood samples of three Malays and two Indian siblings, ranging from 12 to 45 years old. All of them have myotonia and progressive muscle weakness, while some have ptosis, cataract and atrial flutter. Muscle biopsies were carried out at Hospital Kuala Lumpur for the two Indian siblings and the results were suggestive of myotonic dystrophy. To confirm the diagnosis of DM1, we used a combination of fluorescent PCR (F-PCR) and triplet-primed PCR (TP-PCR), followed by capillary electrophoresis. *Results:* Initial screening by F-PCR showed the presence of an allele with approximately 5-13 CTG repeats which fall in the normal size range. TP-PCR further identified large expansions, indicating the presence of pathogenic alleles with ≥50 repeats in four patients, including the two Indian siblings. The expansions confirmed the diagnosis of DM1 in these patients. *Discussions:* Almost all individuals with DM1 inherited their expanded allele from a parent with an abnormal range (>34 repeats), who may or may not appear to be affected. With the establishment of DM1 molecular testing in Institute for Medical Research, DM1 cases could be diagnosed swiftly and accurately. Furthermore, molecular testing is less invasive compared to muscle biopsy. Correct diagnosis is not only important for the treatment and management of the patient, but also pivotal for genetic counselling and early diagnosis of at-risk relatives.

GEN03 Same abnormalities, different manifestation: A rare case report of maternally inherited partial Xq duplication in syndromic baby

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Introduction: Xq27 to Xq28 duplication syndrome is an X-linked severe neurodevelopmental disorder in males. Most females are asymptomatic carriers with phenotypic heterogeneity due to X-chromosome inactivation (XCI) mechanism. Herein we report a case of an infant with syndromic features associated with maternally inherited derivative X chromosome involving duplication of Xq27 to Xq28. *Case report:* A 13-months-old boy was referred to rule out Prader Willi Syndrome. He was born preterm at 36 weeks with birth weight of 1.5kg. This infant was presented with IUGR, severe laryngomalacia, pulmonary hypertension, feeding problem, scrotal hypoplasia, undescended testis and short stubby fingers before he passed away at 15 months of life. Initial cytogenetics finding revealed the presence of additional material on chromosome Xp which was later identified by molecular cytogenetics (FISH) study to be derived from X chromosome material. Further investigations revealed that the phenotypically normal mother carries the same rearrangement on one of her X chromosomes. Chromosomal microarray analysis later delineates the duplicated material to originate from Xq27.2 to Xq28 region with size of 13.488Mb. Discussion: In males, X-chromosome duplications lead to functional disomy of the genes located within the

duplicated segment. Conversely, female carriers are usually asymptomatic because these rearrangements result in a skewed X- inactivation phenomenon. Further investigations such as XCI should be performed to determine its pattern for female carriers and pathogenicity of genetic variant in an X-linked gene. Since the mother carries a risk of having abnormal children, prenatal testing should be considered in future pregnancies.

GEN04 DiGeorge syndrome involving deletion of only DGCR6 and PRODH not detectable by FISH : A rare case

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Introduction: DiGeorge syndrome is one of the most common microdeletion syndromes, also known as 22q11 deletion syndrome or velocardiofacial syndrome (VCFS). It is seen in 1 in 2000 to 4000 live births in Malaysia. The pathophysiology of this syndrome is due to microdeletion of about 1.5 – 3Mbp of the DiGeorge Critical Region (DGCR) which is located on the long (q) arm of chromosome 22 at region 22q11.2. Current standard method of investigations involve conventional cytogenetic followed by FISH technique. *Case report:* A 2-year-old girl born premature at 35 weeks was noted to have bronchopulmonary dysplasia, recurrent aspiration pneumonia, multiple cardiac anomalies, and developmental delay. Her blood sample was sent for conventional cytogenetics and FISH for deletion 22q11.2. Both tests were normal. Subsequently, array CGH test was sent to rule out microdeletion syndrome revealed a pathogenic variant of interstitial deletion involving 8 probes at 22q11.2 with the size of 120.37Kb described according to ISCN as arr[hg19] 22q11.21(18890162_19010531)x1. This deletion interval contains two OMIM Morbid genes (*DGCR6* and *PRODH)* located within the known disease critical region for "DiGeorge Syndrome" according to OMIM #601279. *Discussion:* Common FISH probes available in the market for DiGeorge syndrome can detect deletion at either TBX1, TUPLE or N25 loci, which represent the DGCR. However, DGCR6 and PRODH genes, being centromeric to the previously mentioned genes are not covered and this explains the negative result by FISH method. We suggest cases that are strongly suggestive of DiGeorge syndrome be followed up by array CGH test to rule out deletion of DGCR at other loci.

GEN05 Discordance between noninvasive prenatal testing and cytogenetic analysis: Prince Court Lab experience

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Introduction: Non-invasive prenatal testing (NIPT), using the cell-free DNA in maternal plasma, is revolutionising prenatal screening for the common aneuploidies (trisomy 13, 18, and 21). It has been shown that in NIPT, there is a small chance of a false-positive or false-negative result. This is partly due to the placental origin of the cell-free fetal DNA which is not always representative for the fetal karyotype. Therefore, a positive NIPT result should always be confirmed with invasive testing, preferably amniocentesis, in order to investigate the fetal karyotype. *Materials and Methods*: In this study, concordance of results among cases with noninvasive prenatal testing referred for cytogenetics prenatal studies by karyotyping was evaluated. A total of 95 noninvasive prenatal testing-positive cases amniotic fluid samples were received over eighteen months period from January 2021 to June 2022. *Results*: Cytogenetics results were positive for trisomy 21 in 48 of 50 cases (true-positive rate: 96%) and for trisomy 18 in 11 of 16 noninvasive prenatal testing-positive cases (true-positive rate: 69%). True-positive rate was 43% for trisomy 13 and 42% for sex chromosome aneuploidy (includes XXX, XXY, XYY and XO). *Discussion*: This finding suggests that NIPT has high sensitivity and specificity for Down syndrome, with slightly lower sensitivity for Edwards, Patau syndrome and also sex chromosome aneuploidy. Consequently, NIPT results should never be considered in isolation. Diagnostic testing such that karyotyping as the gold standard and further follow-up test using high resolution SNP microarray analysis and Next Generation Sequencing (NGS) is recommended to confirm high risk results.

GEN06 Rare case of female ornithine transcarbamylase deficiency with spontaneous mutation: A case report

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Introduction: Ornithine transcarbamylase (OTC) deficiency is an X-linked inherited disorder characterised by complete or partial lack of the OTC enzyme causing accumulation of ammonia resulting in neurological/neuropsychological complications. The clinical picture in heterozygous female is highly diverse. Approximately 20% of female carriers of the *OTC* gene are symptomatic. *Case Report:* An 18-months old girl from a non-consanguineous parents presented with sudden onset fever, seizure, lethargy, vomiting and coma. She was found to be drowsy with hyperreflexia and hepatomegaly. MRI brain showed diffuse symmetric bilateral cortical abnormalities suggestive of encephalitis. Routine test showed hyperammonemia, metabolic acidosis (high anion gap) and transaminitis. Plasma amino acid (PAA) showed elevation of glutamine, low arginine and borderline low

citrullinelevel with marked elevation of urinary orotic acid and presence of uracil, suggestive of UreaCycle Defect. Patient was treated accordingly and responded well. Molecular confirmation for OTC gene analysis showed heterozygous *OTC* with no significant evidence of unilateral X-inactivation. Molecular parental screening showed no mutation of *OTC* gene. *Discussion:* This interesting case demonstrated that a previously asymptomatic heterozygous female proband developed a sudden severe hyperammonemic coma, after a stressful event. According to literature, spontaneous mutations rate in female proband can be up until 67%. Female OTC can have mild cognitive impairments and deficits in executive function and finemotor tasks even when exhibiting normal IQ on neuropsychological testing and can be catabolic at pregnancy. Thus, long-term treatment by clinical geneticist is crucial to aim at promoting growth and development and preventing hyperammonemic episodes.

GEN07 Utility of ploidy fluorescence *in-situ* hybridisation and immunohistochemistry of TSSC3 infacilitating the diagnosis of partial and complete hydatidiform mole

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Introduction: Hydatidiform moles (HMs) are pregnancies marked by aberrant development of both embryonic and extraembryonic tissues and are linked to the misexpression of imprinted genes. Partial hydatidiform moles (PHMs) are triploid, with an additional set of chromosomes of paternalorigin, as opposed to complete hydatidiform moles (CHMs), which are mostly diploid andandrogenetic. Due to high morphologic overlaps and inter-observer variability, morphologic examination may not be sufficient for the diagnosis and classification of HMs. The purpose of thisstudy is to assess the contribution of ploidy analysis by fluorescence in situ hybridization (FISH) and immunohistochemical (IHC) analysis using TSSC3 immunomarker in refining the diagnosis of HMs. *Materials & Methods:* A total of 61 histologically diagnosed HM samples consisting of 29 CHMs, 15 PHMs and 17 non-molar abortuses (NMAs) were retrieved from our archive. These samples were subjected to ploidy analysis by FISH utilising centromeric X- and Y-chromosome probes and evaluated by TSSC3 IHC analysis. *Results:* Ploidy analysis revealed that all 29 CHMsand 17 NMAs are diploids, whereas 15 PHMs are triploids. Positive cells for TSSC3 IHC were observed predominantly in the cytoplasm of the villous cytotrophoblasts of all 15 (100%) PHMs and 17 (100%) NMAs. TSSC3 immunoreactivity was undetectable in 25/29 (86.2%) CHMs, withthe remaining four (13.8%) CHMs expressing weak TSSC3 immunopositivity. *Discussion:* WhileFISH separates PHMs with a triploid chromosomal complement from CHMs and NMAs, the silencing of TSSC3 immunoexpression in CHMs offers a practical method for diagnosing molar lesions. The use of these ancillary approaches could raise the level of confidence in the diagnosisand classification of HMs.

GEN08 Point-of-care genetic testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency as a novel molecular diagnostic approach: Challenges and opportunities

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Introduction: Since the emergence of clinical genetics, significant technological innovations have catalysed the diagnostic approach and molecular classification of diseases including glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked genetic disorder that may cause acute haemolytic anaemia and severe neonatal hyperbilirubinemia. Current developed G6PD point-of-care tests (POCT) were limited to qualitative and quantitative methods, while the molecular assays which are often needed to complement the clinical acumen are complex, labourious, and limited to advance laboratory settings. This review examines the challenges and opportunities towards developing a genetic POCT as a new frontier in diagnosing molecular variants of G6PD deficiency. *Materials & Methods:* An extensive review of two scientific databases (ScienceDirect and Pubmed) was undertaken to identify studies related to genetic POCT for clinical applications. Reviews, research articles, and conference abstracts are all eligible for inclusion. A discourse analysis was conducted, and a narrative review was provided by outlining key challenges impeding technology adoption and innovation opportunities. *Results:* Successful point-of-care genotyping was recorded for diseases including chronic myeloid leukaemia, aminoglycoside-induced ototoxicity, and pharmacogenetics of medications in acute coronary syndromes. Fundamental barriers were categorised into three main headings; technical, public policy, and economic. Two areas of research opportunities were highlighted; the development of a lab-on-chip device for common G6PD molecular variants and a G6PD allele scoring software. *Conclusion:* Point-of-care genetic testing has many advantages over conventional molecular assays and other point-of-care instruments. The development of a compact and portable genetic POCT will help clinicians in the rapid identification of clinically relevant G6PD variants.

GEN09 A peek in a small genetic pool: A case report

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Introduction: 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency also known as HMG CoA Lyase deficiency is an uncommon inherited disorder in which the body cannot process a particular protein building block (amino acid) called leucine. It is a rare autosomal recessive genetic disorder that usually appear within the first year of life and usually characterised by episodes of severe hypoketotic hypoglycemia, accompanied by vomiting, diarrhoea, dehydration, hepatomegaly and lethargy that finally can progress to life-threatening coma. Episodes are often triggered by infection, fasting, strenuous activity or other types of stressor. *Case Report:* A 7-month-old Orang Asli infant was brought to the nearest health facility for rapid breathing, runny nose and loose stool; 11 hours before he succumbed to death. He had backgrounds of bronchopneumonia and sepsis when he was 4 and 5 months old. Abnormal autopsy findings include haemorrhagic lungs, hepatosplenomegaly with yellowish coloured liver. Histopathology examination suggestive of bronchopneumonia and the liver showed severe steatosis with loss of normal architecture. Other organs were unremarkable. Inborn error of metabolism screening report was suggestive of HMG CoA lyase deficiency. *Discussion:* There is a small genetic pool in the Orang Asli community because of consanguineous marriage. Therefore, we highly recommend for a thorough inborn error of metabolism screening in infants of Orang Asli. It is a simple test which can save life. This is a small step towards precision medicine.

GEN10 A pilot study to determine the association between rs10965215 of ANRIL gene with significant coronary stenosis among cardiovascular disease subjects from a small medical institution

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Introduction: Previous studies have shown that variant rs10965215 in ANRIL gene contributed to an increased risk of myocardial infarction (MI). There have not been any genetic data on *ANRIL* associated with an increased rate of MI in the Malaysian population. This study aims to identify the genotypes of rs10965215 and determine its association with significant coronary stenosis in CVD patients. *Materials & Methods:* Subjects who had undergone coronary angiography at UiTM Medical Specialist Centre were recruited. A single nucleotide polymorphism (SNP), rs10965215, within the *ANRIL* was genotyped using rhAmp SNP genotyping polymerase chain reaction. Data analysis was performed using SPSS Version 28.0. Descriptive statistics were done to summarize the characteristics of the subjects and logistic regression analysis was used to determine the association between genotypes of rs10965215 and coronary stenosis. *Result:* A total of 70 subjects were recruited, in 47 (67.1%) of them had significant coronary stenosis and 23 (32.9%) had normal angiogram. Genotyping of the subjects in the case group showed 57.4% were homozygous AA, 38.3% were heterozygous AG and 4.3% were homozygous GG. The logistic regression analysis showed no significant (crude and adjusted) association between genotypes of rs10965215 and coronary stenosis ($p>0.05$). *Discussion:* This pilot study in our institution did not show significant association between genotypes of rs10965215 and coronary stenosis. This may be explained by the limited sample size. Future research should be conducted using a larger sample size to further analyse the association of different SNPs in *ANRIL* as genetic markers of MI.

GEN11 Acute intermittent porphyria with novel HMBS gene mutations

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Introduction: Acute intermittent porphyria (AIP) is a rare heterogenous autosomal dominant inborn error of metabolism caused by deficiency of porphobilinogen (PBG) deaminase, the third enzyme in the heme biosynthetic pathway due to mutation in the HMBS gene. This study describedthree unrelated patients of AIP cases diagnosed in Malaysia. All three patients showed different clinical presentation. Different variants of HMBS gene were found in these patients. *Case report*:All three patients presented with increased excretion of PBG and total porphyrin (TP), but only two patients had elevation of 5-aminolevulinic acid (D-ALA). The first case is 24 years old female,presented with severe lethargy and headache, with severe hyponatremia. The second case is 22 years old female, presented with acute abdominal pain, abnormal behaviour, seizure and opisthotonos. The third case is a 62 years old female, presented with only photodermatitis. DNA sequencing revealed two novel variants; c.503G>T p. (Glyl68Val)

in exon 10 and c.88-8_89del p.(?) in intron 3 which are predicted as pathogenic, whereas one variant c.423-3C>T p.(?) in intron 8 is classified as variant of uncertain significance (VUS) due to its presence in gnomAD populationdatabase. *Discussion*: These cases illustrate the heterogenous clinical, biochemical and molecularfindings in patients with AIP. Interestingly, patient 3 had the least severe clinical presentations andmild elevation of uroporphyrins and the intermediates. D-ALA which is usually elevated in patients with AIP, is also normal in this patient, hence, need further molecular investigation.

GEN12 Seven novel variants in UBE3A gene from Angelman syndrome patients: Thirteen years of experience

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Introduction: Angelman Syndrome (AS) is caused by lack expression of the maternally inherited UBE3A gene in the brain, due to either deletion of 15q11q13 on the maternal chromosome, paternal uniparental disomy, imprinting defect or mutation in UBE3A gene. AS is characterised by severe developmental delay, severe speech impairment, gait ataxia and/or tremulousness of the limbs and a unique behaviour with an inappropriate happy demeanour including frequent laughing, smiling and excitability. Our objective is to identify AS by methylation analysis on the 15q11q13 and DNA sequencing analysis in the UBE3A gene. *Material & Methods:* DNA was extracted from blood-EDTA, received from approximately 1,100 patients with clinical symptoms of AS between April 2009 and April 2022. Methylation Specific-PCR (MS-PCR) was initially carried out from 2009 and replaced by Methylation Specific-Multiplex Ligation Dependent Probe Amplification (MS-MLPA) in 2015 to date. Patients with negative result by MS-MLPA were proceeded with UBE3A gene sequencing upon request by the clinical geneticist. DNA sequencing data was analysed using SeqScape software to identify the variants and pathogenicity of variant was predicted using VarSome software. *Results:* From 132 confirmed AS patients, 61 were detected by MS-PCR, 63 by MS-MLPA and 8 by UBE3A gene sequencing. Seven of the eight variants were novel (c.1250G>A, c.1517G>A, c.172A>T, c.2500A>G, c.2503_2508del, c.2513_2514delGA and c.478_481delGCAA). Three novel variants were predicted as pathogenic while four were likely pathogenic. *Discussion:* The MS-MLPA is currently the gold standard for diagnosis of AS. Besides providing accurate diagnosis of AS, it can determine the cause of the disease which is important for recurrent risk assessment.

GEN13 Novel mutations of the arylsulphatase B (*ARSB*) gene in Malaysian patients with mucopolysaccharidosis type VI

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Introduction: Mucopolysaccharidosis (MPS) type VI or Maroteaux-Lamy syndrome is an autosomal recessive lysosomal storage disorder characterised by ARSB enzyme deficiency. The enzyme deficit causes a pathological accumulation of glycosaminoglycans dermatan-sulphate and chondroitin-sulphate resulting in harmful effects on various organs and short stature. The goal of this study is to characterise *ARSB* mutations in 16 MPS VI patients who were referred to the Institute for Medical Research between 2016 and 2021. *Materials & Methods:* Mutation screening in blood-derived DNA was performed using PCR-Sanger sequencing method, which included the analysis of eight exons and exon-intron boundaries. The identified variants were assessed against several public databases and *in silico* prediction tools such as VarSome in accordance with ACMG guidelines. *Results:* A total of seven variants were identified, three of which were novel missense variants p.(Arg327Gln), p.(Ala431Asp), and p.(Pro523His) that were not found in gnomAD database. Varsome predicted these variants as likely pathogenic because the nucleotide position was strongly conserved with pathogenicity scores of 93-95% from multiple in-silico predictors. The remaining four variants were known mutations that were listed in HGMD, including two missense mutations p.(Phe399Leu) and p.(Trp450Leu), one nonsense mutation p.(Arg191*) and one deletion mutation p.(Ala39Profs*80). *Discussion:* Our study broadens the spectrum of *ARSB* mutations, thus contributing to the knowledge of mutational signatures in MPS VI. Once the diagnosis of MPS VI is confirmed, enzyme replacement therapy (ERT) could be used as treatment for the patient. ERT treatment may slow down or prevent significant pathological changes of the disease.

GEN14 Isochromosome mosaic Turner syndrome in two Malaysian patients

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Introduction: Isochromosome mosaic Turner syndrome (IMTS) is a variant form of Turner syndrome with karyotype showing one or more additional cell lineages other than 45,X, along with the presence of a structurally abnormal X chromosome of either two short or two long arms. It has a broad range of clinical phenotypes with prevalence of 15-18% among females with Turner syndrome. Here we present two cases of IMTS with karyotype of 45,X/46,X,i(X)(q10). *Case report*: A 3-year-old girl was diagnosed with bilateral developmental dysplasia of the hips at birth. Her subsequent follow up showed signs of failure to thrive and global developmental delay with bilateral conductive hearing loss. Physical examination did not show any gross dysmorphism except for unilateral cleft palate and bilateral developmental dysplasia of the hips where she was treated with Pavlik harness and hip spica. The second case is a 23-year-old lady who presented with primary amenorrhoea with features suggesting of classical Turner syndrome. Hormonal profile demonstrated elevated LH (luteinizing hormone) and FSH (follicular stimulating hormone) with reduced oestradiol level. Abdominal ultrasound revealed absent ovaries with infantile uterus. She was started on oestrogen replacement therapy with progesterone in order to induce puberty and will be on lifelong combined hormonal replacement therapy. *Discussion*: These cases highlighted the significance of karyotyping analysis in detecting IMTS among patient who presented with atypical or milder form of classical Turner syndrome. Early diagnosis is crucial in order to minimise the physical and psychosocial challenges associated with Turner syndrome.

GEN17 Coinheritance of Hb Adana with Hb Constant Spring: A case report

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Introduction: Point mutation of codon 59 of either alpha 1 or alpha 2 gene leads to the formation of Haemoglobin (Hb) Adana, due to the substitution of amino acid Gly→Asp. In the carrier state, the diagnosis of Hb Adana is challenging as the protein is not detectable on routine haemoglobin analysis. Coinheritance of Hb Adana with alpha thalassaemia (either deletional or non-deletional) have varied phenotypic features. *Case report:* An eight-month-old female infant presented initially at three months of age with severe anaemia and hepatosplenomegaly, requiring intermittent blood transfusion. Capillary electrophoresis revealed low Hb A (86.9%), raised Hb F (9.2%) and an abnormal peak at Zone C (2.4%). Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS PCR) revealed co-inheritance of Hb Constant-Spring and Hb Adana, whilst GAP PCR revealed no deletional mutations. Both parents are asymptomatic. Capillary electrophoresis of her father showed small peak at Zone C (0.6%) with heterozygous Hb Constant Spring detected on ARMS PCR. Haemoglobin analysis of her mother revealed no abnormality, however, non deletional missense mutation of codon 59 was detected on ARMS PCR. No deletional mutation was detected on GAP PCR for both parents. *Discussion:* The phenotype of patients with coinheritance of Hb Adana with other alpha thalassaemia are varied, and largely depends on whether alpha 1 or alpha 2 gene is affected. Codon 59-point mutation affecting alpha 2 gene has generally more severe phenotype. Gene sequencing has a role to identify which alpha gene is affected, for prenatal screening and to predict disease severity.

GEN18 Effect of prebiotic on hepatocellular carcinoma-induced intestinal inflammation in zebra fish

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Introduction: While the interaction between hepatocellular carcinoma (HCC) and its systemic effect has been well studied, the effect of intestinal microbiota on HCC's systemic effect still lacks data. Mannan oligosaccharides (MOS) is a type of functional oligosaccharide which have received increased attention because of their beneficial effects on intestinal health. In this study, we focused on the alterations in the intestinal inflammation after the introduction of experimental diet which includes MOS in xmrk induced fish. *Materials & Methods:* Adult male wild-type (wt) and xmrk zebrafish were fed with fishmeal mixed with 0.6% of MOS for 4 weeks. Then, zebrafish gut samples were cryosectioned, immunofluorescent-stained and imaged for the number of neutrophil per target area of each of part of the intestine which includes Intestinal Bulb (IB), Mid-Intestine (MI) and Caudal Intestine (CI), were calculated. *Results:* Although there was no clear distinction in the correlation between xmrk MOS fish and xmrk fish in overall result, there was a significant difference in the neutrophil count per area given in IB between xmrk MOS fish and xmrk fish. *Discussion:* Although there was no significance between wt MOS fish and wt fish, a trend of low neutrophil count per area given can be noticed in wt MOS fish compare to wt fish in all the result. Thus, more study should be done on the short-term effect (4 weeks in this study) of MOS on HCC induced intestinal inflammation is needed. Overall the result suggests that the short-term effect of MOS is significant in xmrk fish compare to wt fish.

GEN19 Malaysian case of glycogen storage disease type VI: Case report

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Introduction: Glycogen storage disease (GSD) type VI is one of the rare variants of GSD. It is characterised by PYGL mutation leading to liver phosphorylase deficiency and causing glycogenolysis disorder. Classic manifestations are mild hypoglycemia, abdominal distension, growth retardation, hepatomegaly, elevated liver transaminases, hyperlipidemia and generally normal lactate and uric acid. *Case report:* This patient is a 1-year-old Malay girl who was the second child out of non-consanguineous parents. She was born full term and weighed 2.4 kilograms. She was referred for incidental finding of hepatomegaly with deranged liver enzymes. Physical examination showed no growth retardation and per abdomen showed hepatomegaly (4 cm below the right costal margin). Laboratory tests revealed significantly increased liver transaminases, hyperlipidaemia and slightly decreased glucose. Liver biopsy result was consistent with GSD. Sequence analysis test revealed two pathogenic heterozygous mutations identified on PYGL gene which are splice site c.772+2_772+3del and missense c.2071G>C (p.Gly691Arg). Following treatment with uncooked cornstarch four times per day, all biochemical parameters were normal. Family screening of mother and younger brother exhibits both are carriers of missense mutation of c.2071G>C(p.Gly691Arg). *Discussion:* According to Human Gene Mutation Database, there are around 50 mutations associated with GSD type VI. Missense and splice site mutations are the major PYGL mutation types that been reported. In this report, there were two pathogenic mutations of PYL gene c.772+2_772+3de (splice site) and missense c.2071G>C(p.Gly691Arg). Genetic testing helps patients better understand their conditions and direct them toward genetic counselling for hereditary diseases.

GEN20 Urinary profiling of HMG-CoA synthase deficiency based on Malaysian cases

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Introduction: Mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase deficiency is a rare autosomal recessive metabolic disorder in which hepatic ketogenesis fails during illness or fasting. The purpose of this paper is to highlight the pathologic metabolites of HMG-CoA synthase deficiency in urine organic acids profile that people tend to miss out and misdiagnose as Glutaric aciduria type 1 (GA-1) or fatty acids oxidation defects (FAOD). *Materials & Methods:* Urine organic acids were extracted via liquid-liquid extraction with ethyl acetate, then derivatised into trimethylsilyl group and analysed using GC 7890B / MS 5977A equipped with a DB-1 GC column. *Result:* The urine organic acids profile in 4 patients showed significant increased excretion of glutaric acid with the presence of 3-hydroxy glutarate which may look like a typical GA-1 profile but the presence of ketones and dicarboxylic acids with prominent elevation of adipate, dominating the profile and reflecting fatty acids oxidation defects (FAOD). Small but significant peaks of 4-hydroxy-6-methyl-2-pyrone, 5-keto-3-hydroxy hexanoate, 3,5-dihydroxy hexanoate and 3,5-dihydroxy hexanoic lactone were also observed in all patients. *Discussion:* In HMG-CoA synthase deficiency, the urine organic acids profile resembles GA-1 and FAOD but the pattern was unusual due to the presence of excessively excreted adipate with the presence of small but significant peaks of 4-hydroxy-6-methyl-2-pyrone, 5-keto-3-hydroxy hexanoate, 3,5-dihydroxy hexanoate and 3,5-dihydroxy hexanoic lactone.

GEN21 Carnitine-acylcarnitine translocase deficiency (CACTD): A rare disease detectable by LC-MS/MS

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Introduction: Carnitine-acylcarnitine translocase (CACT) deficiency is a rare autosomal recessive disorder of fatty acid β-oxidation caused by functional defects of translocase protein in inner mitochondrial membrane. *Case report:* A male infant, the first child of non-consanguineous parents, was delivered at 38 weeks by C-section with birth weight of 2.36 kg, length of 47 cm and occipital frontal circumference of 33 cm. He manifested with neonatal onset of hypoketotic hypoglycaemia, hyperammonaemia and mild metabolic acidosis in the first 48 hours of life. He had hypocalcaemic seizure, coagulopathy, cardiomyopathy and hepatomegaly with transaminitis. *Discussion:* Initial laboratory investigations showed profound hypoglycemia (0.05 mmol/L), hyperammonemia (265 mmol/L), elevated creatine kinase (567 μ/L), low ionised calcium (0.59 mmol/L) and elevated transaminases. Plasma glutamine was normal, and urine organic acid analysis showed elevated dicarboxylic acids. Blood spot acylcarnitine profile demonstrated a significantly abnormal accumulation of several long chain acylcarnitines including C14, C16, C18 and C18:1 with an increased in (C16 + C18:1)/C2 ratio and marginally low C0, a typical pattern consistent with a

diagnosis of either CACT or CPT2 deficiency. Whole exome sequencing identified a homozygous pathogenic splice site variant c.199-10T>G in the *SLC25A20* gene. Screening of DBS for metabolic diseases using LC-MS/MS would be one of the earliest clues especially if it is associated with neonatal hyperammonaemia and hypoglycaemia, which in turn may provide accurate therapeutic interventions and adequate caloric consumption to prevent severe decompensation and multisystem organ failure that could lead to death.

GEN22 A streamlined targeted NGS workflow for comprehensive genomic profiling of tumour samples

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Introduction: Next-generation sequencing-based (NGS) molecular tumour profiling has provided extensive value for personalised cancer therapy. Compared to conventional low-throughput technologies such as FISH and PCR, NGS enables comprehensive and simultaneous identification of genomic alterations that help to expand and inform treatment options, advance the development of new therapies and ultimately improve patient outcomes. *Methods:* We developed manual and automated OncoKey® SL Plus workflows comprising DNA and RNA extraction from formalin-fixed paraffin-embedded (FFPE) samples, library preparation and dual UDI-UMI hybrid-capture target enrichment. Our pan-cancer OncoKey SL 60 Plus and 525 Plus panels cover 60 and 525 clinically relevant genes respectively, and 10 oncogenic pathogens. Sequencing was performed on Illumina® MiSeq, NextSeq and Novaseq Systems. Secondary analysis and clinical interpretation reports were generated using proprietary Vela SQ Reporter® and Vela Analytics® software respectively. *Results:* In this study, we used highly characterised reference materials from SeraCare and Horizon Discovery. With just 40 ng of nucleic acid, we demonstrated robust detection of 100% of the expected single nucleotide variations (SNVs), insertions/deletions (INDELs), copy number variations (CNVs), microsatellite instability (MSI), fusions, splice variants, accurate tumour mutation burden (TMB) scores, and spiked-in oncogenic viruses and bacteria. We achieved a LOD of 5% DNA VAF and 100% analytical sensitivity and specificity, with a 5-day turnaround time and less than 2.5 hours of hands-on time from sample to result using the automated workflow. *Discussion:* OncoKey® SL Plus workflow is a cost-effective and accurate diagnostic platform with high reproducibility and sample traceability, providing actionable insights in a streamlined NGS workflow.

GEN23 The genetic evaluation of mitochondrial DNA (mtDNA) variants in Malaysia shows high incidence of m.3243A>G among patients with clinically suspected MELAS syndrome

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Introduction: Mitochondrial disorders are among the most common and complex of all inherited genetic diseases. Diagnosis are challenging due to diverse clinical spectrum and highly heterogeneous genotypes involving both mitochondrial and nuclear genome. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the most common mitochondrial disorders (1 in 4000) frequently caused by m.3243A>G mutation. Here we presented our experience in identifying mtDNA variants among patients who clinically suspected of MELAS syndrome. *Materials & Methods:* About 677 patients with suspected MELAS referred for molecular investigation from 2011-June 2022 were included in this retrospective cohort study. Genomic DNA extracted from blood, urinary sediment and muscle biopsy using a standard procedure. Molecular testing performed by PCR and Sanger sequencing. *Results:* We identified 67 from 677 patients (10% positive rate) with MELAS mutations. The MT-TL1:m.3243A>G was the most common genotype (91%) followed by MT-TLI:m.3252A>G (4.4%), MT-NDI:m.3481A>G (2.9%) and MT-TL1:m.3271T>C (1.4%). Patients' age ranged from 5 to 56 (mean 20.6). Mutation load ranged from 15%-85% in blood and higher in urine and muscle. A further 51 cases were identified via family screening, nearly 1/3 of them have symptoms. *Discussion:* The m.3243A>G is the most common mutation in our cohort, consistent with most previous reports. MELAS testing should include genes other than MT-TL1 and urine is the preferable non-invasive sample. Identification of a causative mutation allows patients to end their diagnostic odyssey; enable more specific treatment and surveillance of new symptoms. Family screening may reveal individuals who have high mutational loads and are thus at risk of developing symptoms.

GEN24 Haplotype analysis reveals a possible founder effect of a novel *BSCL2* mutation c.567_573+1dup in two Malaysian families with congenital generalized lipodystrophy

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Introduction: Congenital generalised lipodystrophy (CGL) is a clinically and geneticallyheterogeneous condition characterised by extreme paucity of adipose tissue at birth. Four individuals with characteristic features of CGL from two independent Sarawakian families in Malaysia were investigated in our previous study. They were homozygous for a novel duplication mutation c.567_573+1dup in the *BSCL2* gene predisposing to CGL type 2. The observation of the same mutation in two independent families suggested a common origin. Therefore, we speculated that this mutation was probably a founder mutation. *Materials & Methods:* In this study, we assessed the founder effect for this mutation through haplotype analysis by genotyping the four affected individuals and their parents using six microsatellite markers flanking the *BSCL2* gene (D11S1313, D11S1335, D11S4076, D11S1883, D11S4747,and D11S913). These microsatellite loci were first amplified using the fluorescently labelled PCR primers, followed by fragment separation in genetic analyser. Genotyping of the microsatellite markers was performed using GeneMapper software and haplotypes were constructed manually. *Results:* The microsatellite analysis showed segregation of a unique homozygous haplotype of four consecutive microsatellite markers (D11S4076, D11S1883, D11S4747 and D11S913) surrounding the mutation c.567_573+1dup in all affected individuals, thus consolidating the hypothesis of founder effect for this mutation in Sarawak. *Discussion:* Identification of this founder mutation has important implications towards geneticcounselling for their at-risk relatives besides facilitating the development of cost-effective molecular diagnostic approaches for CGL by screening the founder mutation first. To our knowledge, this is the first evidence in Malaysia for a founder mutation in *BSCL2* gene.

GEN25 Perforated appendicitis in a background of undiagnosed Gilbert syndrome: A case report

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Introduction: Gilbert syndrome (GS) is a benign inherited condition that usually presents with recurrent episode of jaundice due to isolated hyperbilirubinaemia predominantly unconjugated hyperbilirubinaemia in the absence of liver disease or haemolyis. We present a case of mild jaundice presented with perforated appendicitis and subsequently diagnosed with GS. *Case report*: A 24-year-old Malay gentleman presented with right iliac fossa pain, fever, vomiting and loose stool. Clinical examination noted bilateral scleral jaundice, guarded abdomen and positive Rovsing's sign. Blood investigation showed leukocytosis of $19.8x10^3$/uL with predominant neutrophil of 88%, hyperbilirubinaemia of 219 umol/L with predominant indirect bilirubin of 176 umol/L, and no evidence of haemolysis. Ultrasound of hepatobiliary revealed no evidence of biliary obstruction. Perforated appendicitis confirmed and proceeded with laparoscopic appendicectomy. His jaundice was noticed ever since childhood but was never investigated. His mother and maternal aunt were having similar presentation as well. GS mutational analysis was carried out and a homozygous mutation at the c.-3279 T>G(G/G) hotspot of the UGT1A1 gene was found thus confirming the diagnosis of GS. *Discussion:* Early recognition of GS is very important because of relatively mild hyperbilirubinaemia may be mistaken for a sign of occult, chronic or progressive liver disease. Besides, GS is associated with suboptimal metabolism of certain group of drugs, thus undiagnosed individual at risk of exposure to drug toxicity. Early establishment of GS diagnosis therefore may assist treating physician to apply appropriate targeted management for better clinical outcome.

GEN26 Monosomy 7 in adolescent with AML: A diagnostic challenge

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Introduction: Paediatric and adolescent patients presented with myeloid neoplasm harbouring the monosomy 7 (-7) abnormality present as a unique diagnostic challenge. Myeloid neoplasm with germline predisposition has to be considered in these patients. However, due to rarity of these cases combined with heterogenous clinical presentation and complex diagnostic testing, identification of this variant is challenging. We herein report a case of AML in a 13-year-old young girl, suspicious of a monosomy 7 germline predisposition variant and the challenge to identify it. *Case report*: Our patient presented with pancytopenia with 50% blast cells on the background of hypocellular marrow and significant dysplastic changes in erythroid and megakaryocytic lineages. Immunophenotyping was consistent with AML while cytogenetic analysis showed 45,XX,-7 karyotype. She was

planned for haematopoietic stem cell transplantation following remission post chemotherapy, however patient relapsed before the procedure. Further investigations to identify germline variants were not conducted due to limited resources. *Discussion:* Patients with -7 germline predisposition variant may present with bone marrow insufficiency or presented with MDS or AML. Absence of a family or personal history of a hereditary disorder does not exclude the possibility of this condition. The lack of typical syndromic features observed in some patients may be due to de novo mutations and/or variable penetrance and expressivity. For diagnosis in a patient without a known inherited mutation, whole exome sequencing or a targeted multigene panel is recommended (e.g., *GATA2, SAMD9, CEPBA* etc). Some of the mutations are also somatic driver mutations in sporadic MDS/AML, hence in some cases, verification using specialized germline testing on constitutional DNA cells is necessary.

GEN27 Novel mutation in three unrelated PMM2-CDG patients

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Introduction: PMM2-CDG is the most frequent type of congenital disorder of glycosylation caused by deficient of *phosphomannomutase 2* enzyme encoded by *PMM2* gene. PMM2 enzyme catalyzes mannose-6-phosphate to mannose-1-phosphate that will convert to GDP-mannose which transfer mannose to the growing oligosaccharides. It is a rare autosomal recessive metabolic disorder. The prevalence of PMM2-CDG was reported as 1:20000. We report five mutations from three unrelated PMM2-CDG patients for the past 11 years in Malaysia. *Materials & Methods:* A total of 12 CDG type 1 samples received from 2011 to 2021 were sent for *PMM2* gene mutation analysis to our laboratory for confirmatory testing. PCR and direct sequencing of *PMM2* gene (NM_000303.3) were performed to search for the pathogenic variant. In silico analysis using VarSome software was applied to categorise the mutations according to ACMG guidelines. *Results:* Out of 12 patients analyses, three unrelated patients confirmed as CDG type 1a. A total of five *PMM2* mutations were found (c.26G>A, c.338C>T, c.395T>C, c.580C>T) including a novel mutation (c.112A>T). All three PMM2-CDG patients were heterozygous and a recurrent mutation c.580C>T was present in Patient 2 and 3. VarSome analysis categorised four mutations as pathogenic based on criteria (i) reported in ClinVar and UniProt, (ii) located in highly conserved region, (iii) have a deleterious effect by most prediction softwares, and (iv) confirmed by functional study. Whereas, novel mutation is classified as likely pathogenic as the production of null protein and not presented in gnomAD database. *Discussion:* The identification of *PMM2* mutations will expand the spectrum of mutations and also important in genetic counselling.

GEN28 Multiple acyl Co A dehydrogenase deficiency in a syndromic neonate with novel ETFDH mutation

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Introduction: Multiple acyl-CoA dehydrogenase deficiency (MADD; OMIM #231680), is a rare autosomal recessive fatty acid oxidation disorder with heterogenous manifestations from severe neonatal to mild late-onset forms. The clinical disease is based on the electron transfer flavoprotein (*ETFA*, *ETFB*) or ETF dehydrogenase (*ETFDH*) gene mutations. Here, we found ETFDH gene pathogenic variation in a syndromic neonate. *Case report*: A term syndromic baby boy was born with poor Apgar score and multiple congenital malformations. Both parents are non-consanguineous. He was treated for neonatal sepsis requiring intubation. Laboratory investigations showed worsening metabolic acidosis, hypoglycemia and hyperammonemia. ECHO revealed ventriculopathy and USG cranium demonstrated periventricular leukomalacia. Renal ultrasound showed bilateral renal parenchymal disease. Blood acylcarnitine profiles showed elevation of multiple acylcarnitines with free low carnitines. Urine organic acid analysis showed increased aliphatic mono and dicarboxylic acids, acylglycines and glutarate. Gene panel MADD testing on 21 genes including sequencing and deletion/duplication revealed one novel heterozygous pathogenic variant c.1469-1G>T in intron 11 of ETFDH gene. We identified two unreported heterozygous variants, c.607-55T>C and c.1691-39_1691-37dup in intron 5 and intron 12, respectively that may affect mRNA stability. Both are variants of uncertain significance (VUS). He deteriorated on day 2 of life. *Discussion*: MADD is a multisystem disorder with clinical heterogenicity. We identified a novel heterozygous pathogenic variant c.1469-1G>T *ETFDH* gene. However, further functional analysis was not feasible as the child deceased. For this case, we might have missed the medication period. Therefore, timely treatment is essential during this crisis, reflecting the importance of molecular diagnosis for early MADD management.

GEN29 A first reported case of testicular feminization syndrome in two sisters in the northern Malaysia

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Introduction: 'Testicular feminization syndrome' is based upon phenotypic females with a 46,XY karyotype, usually with complete absence of male sexual characterisation. Later, it was renamed androgen insensitivity syndrome (AIS) with the finding of androgen resistance rather than a deficiency. AIS cases were likely to be 1 in 20,000 to 1 in 99,000 genetic males 46,XY. *Case report:* Two sisters, respectively age at 18 and 23 years old presented with primary amenorrhea. The younger of the two siblings was initially thought to have Fragile X syndrome. Blood sample was sent to Advanced Diagnostic Laboratory (ADL) and cytogenetic analysis was done. From G-banding, cells were examined which showed a karyotype of 46,XY suggested that the Y chromosome had normal structure. The polymerase chain reaction (PCR) was carried out as a confirmatory test and showed positive for SRY. Whilst at the age of 23, the older of the two sisters has a height of 164 cm having no menstrual cycle. Cytogenetic G-banding analysis was done at ADL, showing a karyotype of 46,XY. PCR was carried out as a confirmatory test and showed positive for SRY (testis-determining factor). Both siblings were assigned as females. To the best of our knowledge, this is the first reported case of two members from the same family present with 47, XY with female phenotype in the northern Malaysia. *Discussion:* AIS is a common cause of male pseudohermaphroditism, and needs medical, surgical management and also long-term psychological therapy if needed.

GEN30 Improvement of argininosuccinic acid detection on ion exchange chromatography

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Introduction: Argininosuccinic aciduria (OMIM 207900) is caused by deficiency in argininosuccinate lyase (ASL) enzyme that convert argininosuccinic acid (ASA) to arginine in the urea cycle pathway. Severe neonatal onset typically develops hyperammonemia within first few days of life. The clinical presentation is indistinguishable from other urea cycle disorders. Elevation of ASA in plasma and/or urine is pathognomonic. *Case Report:* A baby girl developed encephalopathy, lethargy with respiratory depression at day 3 of life. She was born small for gestational age. Laboratory investigations showed mild metabolic acidosis with hyperlactatemia and hyperammonemia (1260 umol/L). Screening by tandem mass spectrometry (MS/MS) showed hypercitrullinemia. Ion-exchange high performance liquid chromatography (IE-HPLC) revealed marked elevation of plasma citrulline (431 umol/L; 2-30) and glutamine. No ASA peak was seen on the chromatogram, however leucine was unusually elevated (519 umol/L; 15-198). Arginine level was normal. Urine orotic acid was elevated. Initial molecular study showed no mutation of ASS1 gene but subsequent study revealed ASL gene mutation. *Discussion*: Elevation of plasma citrulline is observed in both Citrullinemia type I and Argininosuccinic aciduria but ASA peak would differentiate both the diagnosis. In the initial analysis, ASA had been co-eluted with leucine peak, which is known to be a limitation of IE-HPLC. We have successfully optimised the separation of ASA and leucine on IE-HPLC by increasing the time of the first step of Buffer 3. Analysis of known ASA samples has shown a well separated ASA and leucine. This optimization method is easy to perform as compared to alternative methods.

GEN31 A rare live-born mosaic trisomy 9 co-existing with trisomy 11 in varying proportions

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Introduction: Live-born mosaic trisomy 9 is a rare congenital chromosomal disorder with a great variety in the dysmorphic features and severity correlating to the percentage of cells with an extra chromosome 9 present. We report one rare live-born case with mosaic 47,XY,+9[18]/47,XY,+11[2]/46,XY[40] karyotype pattern, a mosaic trisomy 9 co-existing with trisomy 11 and normal karyotype in varying proportions. *Case report:* The patient was a neonate with salient clinical features of mosaic trisomy 9 such as prenatal growth deficiency, hydrocephalus, myelomeningocele, wide fontanelle, microphthalmia, low-set ears, micrognathia, congenital heart defects comprising of atrial septal defect and ventricular septal defect, and genitourinary anomalies which include hypoplastic genitals and polycystic right kidney. Unfortunately, the baby passed away at 23 hours of life despite conservative management. *Discussion:* Low level mosaicism of trisomy 11 in conjunction with trisomy 9 and normal karyotype in live-born has not been previously reported, this being the first report.

GEN32 Case report: Cystinuria and staghorn calculi in a child

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Introduction: Cystinuria (OMIM 220100) is an autosomal recessive disorder caused by mutation in *SLC3A1* and/or *SLC7A9* characterised by impaired proximal tubular reabsorption of cystine, lysine, ornithine and arginine. High urinary cystine causes renal stones due to low solubility at normal urine pH. Patients usually present with recurrent renal calculi, urinary tract infections and may develop renal failure. Medical management includes high fluid intake, urine alkalinisation and cystine chelating agents. *Case report*: A 2-year-old girl presented with fever, vomiting and urosepsis progressing to acute kidney injury. Both parents are non-consanguineous. She was born at term with milestones appropriate for age. The urine analysis showed increased blood and leukocytes. The renal ultrasound revealed bilateral nephrolithiasis and obstructive uropathy. Computerised tomography urogram showed right staghorn calculus. Her condition improved with antibiotics and hydration. Further laboratory investigations include urine amino acids demonstrating marked excretion of cystine and dibasic amino acids. Urine cystine quantification was 167 mmol/mol creatinine. She underwent ureteric stenting and right percutaneous nephrolithotripsy with no further episodes. Whole exome sequencing detected a pathogenic variant c.730del p. Glu244AsnfsTer20 and a likely pathogenic variant c.265del p. Met89Ter in *SLC7A9* gene. Both parents are carriers for the mutations. Her mother and younger sister also have cystinuria but clinically asymptomatic. *Conclusion*: Cystinuria should be considered in paediatric urolithiasis. Regular follow-up is needed to assess compliance, renal function and early stones detection. Family screening for cystinuria is crucial.

GEN33 First case of guanidinoacetate methyltransferase deficiency in Malaysia: 20 years of challenges in biochemical testing and molecular diagnosis

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Introduction: Guanidinoacetate methyltransferase (GAMT) deficiency (OMIM 601240) is a disorder of creatine biosynthesis, characterised by excessive amounts of guanidinoacetate (GAA) in body fluids, deficiency of creatine (Cr) in the brain and presence of mutations in the *GAMT* gene. *Case report:* 21 year-old female born to non-consanguineous parents. This patient's symptoms began with spastic diplegia and seizures at 6 months-old and progressed to neuroregression, speech regression, behavioural disorders, involuntary movements and ataxic gait. The worsening seizures were refractory to anticonvulsants and associated with occasional hemiplegia and evolved from upperlimb clonic to startle episodes and later myoclonic epilepsy. Her diagnosis remained elusive despite extensive investigations until Magnetic Resonance Spectroscopy (MRS) done at the age of 16 showed a low Cr uptake. Urine sample showed high urine GAA and low urine Cr suggestive of GAMT deficiency. A Whole Exome Sequencing (WES) revealed only a heterozygous GAMT variant c.391+1G>C initially. In 2020, Institute for Medical Research (IMR) had successfully developed new test for urine, plasma and bloodspot using Liquid Chromatography Mass Spectrometry (LC-MS/MS) and new samples sent at the age of 19 showed persistent high GAA and low Cr in all three specimens. Another WES then confirmed a second heterozygous GAMT variant c.327+43G>A hence ratifying the diagnosis. Six months after the initiation of oral creatine monohydrate and ornithine, she appeared to be more alert and her epilepsy was under control. *Discussion:* This case showed that MRS, biochemical testing and WES confirmed the diagnosis of GAMT deficiency and ended the diagnostic odyssey for this patient.

GEN34 Familial 21;22 chromosomopathy: A rare case report

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Introduction: Reciprocal translocation is a type of chromosome rearrangement which occur when there is an exchange of genetic material between two non-homologous chromosomes. In the case where the exchange is balanced, the individual will not exhibit any phenotypic abnormalities. However, when the unbalanced form of the abnormality is transmitted to their offspring, several or more complications can developed. Here, we present a case report of a family of two siblings with global developmental delay and syndromic features associated with maternally inherited unbalanced translocation involving the *ARSA* (Arylsulfutase A) gene. *Case report:* Initial cytogenetics finding of the siblings showed normal karyotype, 46,XY. FISH studies using the Di-George N25 probe showed different results between the two; older sibling has trisomic dosage of ARSA where the extra dosage is located on the distal part of one chromosome 21 while the younger showed deletion of one ARSA gene. Further investigations revealed that the mother carries a balanced reciprocal translocation between chromosome 21 and 22. Each unbalanced form has been passed on to her children. *Discussion:* This finding represent a rare case of deletion/duplication syndrome involving the

ARSA gene which is important in making the enzyme arylsulfatase A. Severe disruption in arylsulfatase A activity can cause metachromatic leukodystrophy, a disorder that causes deterioration of nervous system functions. Since the mother carries a risk of having abnormal children, prenatal testing should be done in future pregnancies. All first degree relatives should also be tested to identify the carriers of this rearrangement.

GEN35 Rapid detection of prenatal aneuploidies by quantitative fluorescent polymerase chain reaction

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Introduction: QF-PCR is increasingly being used in prenatal genetic diagnosis due to its ability to provide rapid and accurate results to women at increased risk of fetal Down syndrome, trisomy 13, trisomy 18, and sex chromosome aneuploidy. *Materials & Method*: We report retrospectively our prenatal aneuploidy QF-PCR results from April-August 2022 performed at the Cytogenetic & Molecular Diagnostics Laboratory, Pantai Premier Pathology, Kuala Lumpur. Amniotic fluid samples were obtained from pregnant women with elevated risk of fetal aneuploidies, high risk of Downs, advanced maternal age or NIPT-high risk. QF-PCR assay with multiplex short tandem repeat markers involving chromosomes 13, 18, 21 and XY was performed on the amniocytes. DNA isolations were made from peripheral blood of mothers who had blood-stained amniotic fluid to rule out maternal cell contamination (MCC). *Results:* The mean reporting time for QF-PCR was 2.83 days. Chromosome aneuploidies including trisomy 18 (Edwards syndrome) and trisomy 21 (Down syndrome) were detected in 16% of the cases, while the remaining were normal. Two cases had MCC. Both karyotyping and QF-PCR results showed 100% concordance. No uninformative results were observed. *Discussion*: QF-PCR offers a real benefit over conventional cytogenetics methods for a rapid and cost-effective prenatal diagnosis. QF-PCR is also useful when there is culture failure or MCC occurs in karyotyping. However, it has a limitation of not being able to detect structural abnormalities and mosaicism of <30%. Hence, QF-PCR can be used as a complimentary investigation to the gold standard karyotyping for effective method for fetal aneuploidy detection in high-risk pregnancies.

GEN37 Hypomethylation with increased PTX3 protein levels is associated with diabetic nephropathy in male patients

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Introduction: Increased plasma/serum PTX3 levels are associated with accelerated atherosclerotic changes and increased albuminuria with endothelial dysfunction in the patients with stage 1 chronic kidney disease in type 2 diabetes (T2D). Epigenetic changes may provide the link for translating environmental exposures into PTX3 variation in patients with diabetes and diabetic nephropathy (DN). We aim to investigate the DNA methylation levels of the PTX3 gene in the Malay population with T2D and DN. *Materials and Methods*: We performed a case-control study involving a total of 27 non-diabetic control (NDC) subjects, 109 T2D and 43 DN patients. Epigenetic analysis of five CpG sites in the PTX3 gene promoter was performed using bisulfite pyrosequencing technology. Plasma PTX3 levels were measured using an enzyme-linked immunosorbent assay. *Results*: DNA methylation levels of the PTX3 gene were gradually decreased from NDC subjects to patients with T2D and DN, both in males and females. Total mean values of the PTX3 DNA methylation levels were significantly decreased in male DN (5.53%) and T2D patients (6.41%) compared to NDC subjects (7.00%) ($p=0.001$). Lower levels of DNA methylation at the PTX3 gene promoter were associated with higher levels of PTX3 protein in DN and T2D patients compared to NDC subjects. However, no significant difference was observed. *Discussion*: Our results showed that hypomethylation of PTX3 gene was associated with T2D and DN in Malays males. The result was supported by the association of the DNA methylation and plasma levels of the PTX3 gene among T2D and DN patients.

GEN38 Case report: Psychosocial impact of delayed diagnosis of familial Duchenne muscular dystrophy (DMD)

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Introduction: Diagnostic odysseys are psychosocially challenging and distressing to the family with affected family members with an undiagnosed condition. We discussed the psychosocial effect of delayed diagnosis of familial Duchenne muscular dystrophy (DMD). *Case report:* IH was referred to the Genetics Clinic, University Malaya Medical Centre at the age of 7 years old, to rule out DMD. He presented with progressive weakness and an unsteady gait. His two younger brothers had high serum creatine kinase (CK) and muscle weakness too. Genetic testing involving a gene panel, whole exome sequencing (WES), MLPA, and RNA sequencing, did not identify any pathogenic variant. Each result disclosure session was done in a non-directive

genetic counselling approach, but parents were upset due to the absence of a firm diagnosis of DMD. In 2021, IH's mother was pregnant. Unfortunately, prenatal testing was not performed. Parents were more anxious after knowing the foetus was a male too. However, they decided to continue the pregnancy. In 2022, whole genome sequencing (WGS) identified a likely pathogenic hemizygous variant c.5448+67A>G in the DMD gene in IH, confirming the diagnosis of X-linked DMD. Parents were relieved but wished they could have had this information earlier, to plan their pregnancy. *Discussion*: Delay diagnosis led to lost opportunities for timely genetic counselling, especially in reproductive planning. It created pressure and distress. The acknowledgment of those emotions during genetic counselling could normalise these feelings. WGS should be considered for the first tier of genetic testing to achieve a diagnosis. However, limited resources and high costs would be the main limiting factors to achieving an earlier diagnosis.

GEN39 The eleven targeted Therapy-related genomic alterations in non-small cell lung cancer (NSCLC)

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*Introduction***:** Lung cancer is still one of the most common cancers and the leading cause of death in Malaysia. The National Comprehensive Cancer Network (NCCN) has recommended for EGFR, KRAS, BRAF, HER2, MET amplification/exon 14 skipping mutations and ROS1, RET, ALK and NTRK gene rearrangements for testing with non-small cell lung cancer (NSCLC) cases. These genes are important biomarkers for targeted therapy in NSCLC. Hence, the objective of this study is to investigate the prevalence of these genes in NSCLC. *Method:* One hundred sixty seven (167) Formalin Fixed Embedded Paraffin Block (FFPE) and Cell Blocks of confirmed NSCLC cases were received at Pantai Premier Pathology Laboratory for Lung Cancer Panel (LCP) testing. Extraction of DNA and RNA were carried out after evaluation of tumour percentage by pathologist. A commercial amplification-refractory mutation kit was used to detect targeted therapy-related genomic variations on the tumour samples. *Results:* A total of 124 (74.3%) cases harbour mutations, with EGFR being the highest at 50.3%, followed by KRAS at 8.4% (KRAS G12C at 42%), HER2 at 3.0%, MET Exon Skipping at 1.8% and BRAF at 0.6%. For gene rearrangements, ALK showed the highest at 5.4%, followed by ROS1 at 3.0% and RET at 1.8%. NTRK gene fusions were not detected. *Conclusion:* The 11 genes panel shows significant relevant genomic alterations that are associated with relevant targeted treatment in NSCLC and is consistent with most studies regarding genetic testing of NSCLC in Asia.

GEN40 Preimplantation Genetic Screening for Aneuploidy (PGT-A) testing: Pantai Premier Pathology Experience

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Introduction: PGT-A, preimplantation genetic testing for aneuploidy (formerly known as PGS), is a genetic testing for the assessment of chromosomal abnormalities on IVF embryos to select chromosomally normal embryo prior to transfer. We examined the chromosomal status by PGT-A testing using the next generation sequencing (NGS) technology and the age group in Pantai Premier Pathology. *Materials & Methods:* A total of 144 embryos from 39 patients who opted for PGT-A in their IVF cycle from February 2022 to August 2022 were included. The patient's age ranges from 25-44 years old. Genomic DNA from the trophectoderm biopsies was extracted and amplified using EmbryoMap Sample Prep System (Vitrolife, UK). PGT-A was performed using NGS technology on the MiSeq Sequencing System (Illumina). Results were interpreted using Embryomap eMap software analysis and diagnosed as euploid, aneuploid or mosaic. *Results:* The overall frequency of aneuploidy was observed to be 36.1% (52/144) whereas the overall euploid rate was 47.2% (68/144) and mosaicism 16.7% (24/144). The aneuploidy rate was 11.5% at maternal age <30 years. The rate increased dramatically to 55.8% in women above 35 years old. High frequency of aneuploidy was observed in chromosomes +22, +19, +14 and -20. There was also incident of segmental aneuploidy involving loss or gain of chromosomal fragments detected at a frequency of 4.9%. *Conclusion:* NGS-based PGT-A testing is the latest technology which enables the detection of embryos with euploid, aneuploidy and chromosomal mosaicism and an effective method to screen the abnormalities. Our findings provide an important information to improve embryo selection for transfer. The results show the embryos abnormalities increased with the age group.

GEN41 Pilot study of child interstitial lung disease in Malaysia using whole exome sequencing

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Introduction: Child Interstitial lung disease (chILD) encompasses a spectrum of rare pulmonary disorders affecting paediatric patients under the age of 2 years. The genetic variants responsible for chILD have not been characterised previously in Malaysia so in this pilot study, Whole Exome Sequencing (WES) was used to identify the mutation spectrum and the genotype-phenotype correlations in 20 patients. *Materials & Methods:* WES was performed using Sophia Genetics chemistry, run on NextSeq 500 (illumina) and the variants were called using the SOPHiA Genetics DDM software. The pathogenicity of the retained variants were classified according to American College of Medical Genetics and Genomics guidelines. Only variants that were pathogenic and likely pathogenic were selected for reporting. Variants of uncertain significance (VUS) was reviewed more carefully using stringent criteria before inclusion. *Results:* Two pathogenic variants, *PTEN* c.802-2A>T was found in 80% and *TTN* c.30683-1 G>T in 50% of our study population. *TTN* causes myopathy with early respiratory failure and chronic obstructive pulmonary disease. *PTEN* is an important biomarkers that regulate multiple processes associated with various chronic lung diseases. Three likely pathogenic variants *PMS2, TSC1* and *TBX* were identified and two VUS, *MUC5B* c.10230A>T that causes susceptibility to idiopathic pulmonary fibrosis and *SFTPA1* c.420 C>T that causes Interstitial Lung Disease 1 were found in 50% of our patients. *Discussion:* WES is a powerful technique that identified variants causing chILD in our study. VUS were not prematurely disregarded in the analysis because further information and change of classification may become available in the future as more variants are reported.

GEN42 The effect of duration of formalin fixation on immunohistochemical localisation ofoestrogen receptors in breast carcinoma

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Introduction: Breast cancer is one of the most common cancers in women worldwide. Most breast cancersshow overexpression of oestrogen receptors (ERs). The development of drugs to target these hormone receptors, such as tamoxifen, has brought about significant improvement in survival for women with hormone receptor-positive breast cancers. Since information aboutER is vital for patient management, quality assurance is important to ensure accurate testing.The presence of oestrogen receptors as detected by immunohistochemistry (IHC). Most of the tissues used in diagnostic histopathology and IHC are routinely fixed in 10% neutral- buffered formalin. As with ER IHC markers, factor such as duration of tissue fixation for interpretation of positive immunostaining can dramatically affect test accuracy and reproducibility optimal fixation for detection of ER (immunostaining) requires at least more than 6 hours in formalin and cannot be more than 72 hours in fixation. Studies have shown that formalin fixation, especially if prolonged, results in decreased antigenicity, which limits the use of formalin fixed tissues for diagnostic IHC. *Material & Methods:* In this project, 7 Mastectomy sample was collected with a history of breast carcinoma, grossed and the procured tumour was split intomultiple sections for each case and fixed consecutively over various durations which is 4 hours (under fixation), 36 hours (optimal fixation) and 86 hours (prolonged fixation) and all tissue processed and proceed with IHC staining (ER). *Results:* Results showed were oestrogen receptor which had marked decreases in immunoreactivity with in under fixation, and strongimmunoreactivity in standard fixation and intermediate immunoreactivity in prolonged fixation. *Discussion:* In this study duration of fixation reduce the immunoreactivity otherwise did not provide false negative or false positive oestrogen receptor IHC results.