Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

Annual Report 2021

NSW GOVERNMENT
Sydney
Local Health District

Acknowledgements

The developments and achievements described in this report represent the work of many and were invariably undertaken in difficult circumstances as COVID-19 impacted all facets of life at Sydney Local Health District (the District). I would particularly like to thank the following long-term supporters of the Institute of Precision Medicine & Bioinformatics (IPM&B):

Melissa Cole The first IPM&B Operations Manager. She quickly established a professional modus operandi for work undertaken.

Dr Natasha Luquin The first Chief Scientist who worked generously for the IPM&B while continuing her day job as a Senior Hospital Scientist in the Department of Medical Genomics.

Professor Clement Loy Prior to joining the IPM&B, Clement was always generous with his time and advice on a range of issues relevant to the IPM&B.

Professor David Sullivan Clinical chemist at Royal Prince Alfred Hospital and a strong supporter of the IPM&B as the home for new ideas and diverse membership.

Jeremiah O'Sullivan Clinical Manager for the District's clinical stream for neurosciences, bone, joint and connective tissue, plastics and trauma surgery. Jeremiah (Jerry) provided invaluable advice when complex administrative issues arose.

Jay Jiang District Chief of Staff who always provided advice and support despite often inconvenient timing. He has never faltered.

Dr Teresa Anderson, AM A strong supporter of genomic medicine across the District ensuring that genomic medicine and research are fully integrated into clinical models of care.

Professor Ron Trent
Clinical Director, Institute of Precision Medicine & Bioinformatics
Sydney Local Health District

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Acknowledgement of Country

Sydney Local Health District acknowledges that we are living and working on Aboriginal land. We recognise the strength, resilience and capacity of Aboriginal people on this land. We would like to acknowledge all of the traditional owners of the land and pay respect to Aboriginal Elders past and present.

Our District acknowledges ***Gadigal***, ***Wangal*** and ***Bediagal*** as the three clans within the boundaries of Sydney Local Health District. There are about 29 clan groups within the Sydney metropolitan area, referred to collectively as the great ***Eora Nation***. *Always was and always will be Aboriginal Land*.

We want to build strong systems to have the healthiest Aboriginal community in Australia.

Together under the Sydney Metropolitan Partnership Agreement, including the Aboriginal Medical Service Redfern and in collaboration with the Metropolitan Local Aboriginal Lands Council, Sydney Local Health District is committed to achieving equality to improve self-determination and lifestyle choices for our Aboriginal community.

Ngurang Dali Mana Burudi – A Place to Get Better

Ngurang Dali Mana Burudi — a place to get better, is a view of our whole community including health services, Aboriginal communities, families, individuals and organisations working in partnership.

Our story

Sydney Local Health District's Aboriginal Health story was created by the District's Aboriginal Health staff.

The map in the centre represents the boundaries of Sydney Local Health District. The blue lines on the map are the Parramatta River to the north and the Cooks River to the south which are two of the traditional boundaries.

The ***Gadigal***, ***Wangal*** and ***Bediagal*** are the three clans within the boundaries of Sydney Local Health District. They are three of the twenty-nine clans of the great ***Eora Nation***. The centre circle represents a pathway from the meeting place for Aboriginal people to gain better access to healthcare.

The Goanna or *Wirriga*
One of Australia's largest lizards, the goanna is found in the bush surrounding Sydney.

The Whale or *Gawura*
From June to October pods of humpback whales migrate along the eastern coastline of Australia to warmer northern waters, stopping off at Watsons Bay the traditional home of the Gadigal people.

The Eel or *Burra*
Short-finned freshwater eels and grey Moray eels were once plentiful in the Parramatta River inland fresh water lagoons.

Source: Sydney Language Dictionary

Artwork
Ngurang Dali Mana Burudi — a place to get better

The map was created by our Aboriginal Health staff telling the story of a cultural pathway for our community to gain better access to healthcare.

Artwork by Aboriginal artist Lee Hampton utilising our story.

Dr Anthony Cheong, Genetic Pathologist (left) and **Cassandra Kavanagh**, Hospital Scientist (right), Department of Medical Genomics Laboratory, RPA Hospital

1. Executive summary

The Institute of Precision Medicine & Bioinformatics (IPM&B) was formed in early 2020 to provide a clinically-relevant administrative home for health professionals in Sydney Local Health District (the District) working in, or having an interest in, genomics. The IPM&B's strategic focus is broader with the use of precision medicine to include genomics and, with time, other "omics" as they become relevant to patient care, clinical trials and research activities in the District.

Membership of the IPM&B has grown quickly with expanding educational activities underway, and key appointments to: Bioinformatics (Dr Abdul Baten), Deputy Director and Head of Research (Professor Marina Kennerson), Deputy Director and Head of Education (Professor Clement Loy), Consumer Representative (Dr Alan McPhail) and Genetic Pathologist (Dr Anthony Cheong). Clinical Director, Professor Ron Trent has been well supported by Melissa Cole (Operations Manager) and Dr Natasha Luquin (Chief Scientist).

The growing expertise across clinical, laboratory, research and bioinformatics-based genomics will have long term positive impacts on the delivery of patient and family focused care in the District. The IPM&B is well placed to capture new innovations, engage and educate a broader range of health professionals on the practice of genomic medicine. This will grow precision medicine expertise to address actions identified in the genomic strategic plans developed by Commonwealth and NSW Health Departments, and the District's vision for the future.

An important focus during the IPM&B's first year was the development of an effective communication strategy which, although still in progress, has matured to allow greater interactions in 2022 with more diverse health professionals working in the District. Community engagement will be another priority for 2022.

The IPM&B is a District-based virtual institute which, in itself, is challenging to ensure that opportunities available at both the Royal Prince Alfred and Concord Hospital campuses are identified and supported. New collaborations may need to develop to enhance what are already competitive research activities. However, research competitiveness, in the longer term, also requires the ability to respond rapidly to targeted calls for a variety of new funding programs.

The District has led the way in NSW and Australia in how it integrates its clinical, laboratory, research expertise and infrastructure, while at the same time, not losing sight of the health and well-being of its community as its raison-d'être. This is a very supportive structure for precision medicine which promises an additional dimension to innovative models of clinical care illustrated nicely with the rapid growth of precision cancer.

New initiatives in pharmacogenomics, metabolomics, neurogenomics and broader interactions outside the District are proposed for 2022. As the IPM&B matures, its governance structure will need to be reviewed to ensure it continues to drive innovations in precision medicine.

The District, through the leadership of Chief Executive Dr Teresa Anderson AM, has supported and nurtured some outstanding success stories through its discipline-focused clinical institutes. This certainly adds pressure on the IPM&B to continue this trend and can only happen with the support of all IPM&B members.

Professor Ron Trent
Clinical Director, Institute of Precision Medicine & Bioinformatics
Sydney Local Health District

2. Overview of the Institute of Precision Medicine & Bioinformatics

Introduction

Precision medicine (also called personalised or stratified and even molecular medicine) is an expanding approach to disease treatment and prevention that is based on an understanding of an individual's genetic makeup, and how it interacts with the environment. This provides an additional parameter enabling health professionals to develop models of care or prevention that extend beyond the "one-size-fits-all" approach. Precision medicine has also been described as delivering the right treatment to the right patient at the right time.

An example of precision oncology is the emergence of somatic cell DNA testing in cancer which allows cancers to be diagnosed and classified not by the traditional organ or location but by the underlying DNA genetic defect. Armed with this knowledge, the oncologist can select which therapies (established or experimental) are likely to be the most effective for the genetic defect detected or enrol patients in new clinical trials. This approach has revolutionised the treatment of metastatic melanoma, an important tumour in Australia (more on precision oncology in Section 6 of this report).

With the increasing demands on the health dollar, there is pressure to use expensive therapeutics more effectively. This enables a precision medicine approach for Medicare's Pharmaceutical Benefits Scheme which now requires, for some new subsidised therapies, that their use is linked to DNA genetic testing to ensure that patients who access Pharmaceutical Benefits Scheme subsidised drugs do so knowing that they have the best chance of getting a therapeutic response from the treatment, and/or they are not inherently predisposed to serious adverse events. This linking of a test and a therapy is called co-dependent technology.

Although the practice of medicine has always been "precise", it can now go to the next level by taking into consideration an individual's genetic profile. Genomics is the first cab off the rank for precision medicine. It is expected that other "omics" will emerge. The suffix -omics is increasingly used to include a range of biological products that can be measured in large numbers or even all that are found in a cell/organ/body. Metabolomics, proteomics and transcriptomics are examples of emerging contributors to precision medicine.

Hence, the naming of the Institute of Precision Medicine & Bioinformatics specifically ensures the inclusion of precision medicine in its activities, and allows for other omics to be captured as they emerge into the clinical environment. The term "Bioinformatics" was added to ensure capacity building in clinical bioinformatics remains an ongoing priority.

Genetics and genomics at Sydney Local Health District

We have rapidly evolved through the discipline of genetics (involving single or a small number of genes) to genomics (many or all genes). Royal Prince Alfred Hospital (RPA) and Concord Repatriation General Hospital (CRGH) have had a strong commitment to genetics and then genomics starting with molecular genetic DNA testing laboratories in both locations (Department of Medical Genomics and Department of Molecular Medicine). Next was the development of an adult hospital based Clinical Genetics Service which, at the time, was a first since these services were traditionally located within paediatric hospitals. During the 2000s, genomics moved from being a research tool to one that would impact across many clinical disciplines. An interest in genomics developed in many clinical departments for inclusion into models of care (see Box 1 below) or clinical trials or as a component of research activities both basic and clinical.

The Department of Chemical Pathology at RPA has had a long-standing interest in genetic disorders familial hypercholesterolaemia and the porphyrias. The traditional laboratory based diagnostic tests to detect these disorders are well established, and are still used but are limiting to new models of care that allow more timely interventions for earlier treatment, or more effective preventive measures.

Along came genetics and then genomics which provided these opportunities for:

1. more accurate diagnosis in an affected individual based on the genetic defect causing the above disorders, and
2. detection of the family specific genetic defect in at-risk family members to enable earlier interventions before established heart or vessel disease (familial hypercholesterolaemia) or the protean and often difficult to diagnose complications associated with the porphyrias.

A partnership with Chemical Pathology and the Department of Medical Genomics was formed to allow the development of multi-gene (genomics) testing. This has enabled a new model of care for familial hypercholesterolaemia to include a greater focus on prevention or early intervention and community testing. This work remains an important and ongoing activity with more to come as new therapies are developed. It will be accessible through the Pharmaceutical Benefits Scheme to patients with known genetic defects (co-dependent technology described above). At the same time, the ability to accurately detect the underlying genetic basis for some of the acute porphyrias has allowed the entry of some patients into clinical trials utilising novel gene therapy treatments for severe porphyria disorders.

Box 1: Inclusion of genomics into models of care

Working in Sydney Local Health District

Royal Prince Alfred (RPA) and Concord (CRGH) Hospitals in Sydney Local Health District (the District) share a special ethos – to include both clinical and laboratories services within the one structure so that interactions are optimal. In other local health districts, the laboratory services are aggregated in a separate facility, creating barriers to important opportunities for collaboration and support. Therefore, when NSW Health Pathology took over the administration of public hospital laboratories, there was a complexity created that meant some members of the same department were administered by the pathology service while others continued their administration through the hospital and so were attached to a clinical stream (see below). This arrangement worked in some instances but was problematic for the Clinical Genetics Service at RPA as the service did not have a formal connection with a traditional clinical stream while being administered by NSW Health Pathology.

While the above changes were taking place, the Commonwealth and NSW Departments of Health were capturing the potential of genomics for patient care and research in their five year genomics plans. The *District's Strategic Plan 2018-2023* noted genomics as one of the activities around *responsive, integrated, culturally safe and competent multidisciplinary services.*

Clinical Streams in Sydney Local Health District

Clinical Streams operated at RPA and CRGH well before NSW Health adopted a local health district model. They provide an administrative home for comparable clinical activities, for example the gastroenterology and liver clinical stream, or the respiratory and critical care clinical stream. Some are broader in membership, for example, the District's clinical stream for neurosciences, bone, joint and connective tissue, plastics and trauma surgery. The clinical streams have served the District well and a review was undertaken in 2019. The review report recommended some minor changes on how the clinical streams operated, and the formation of a new renal and urology clinical stream.

The report also recommended the formation of the Institute of Precision Medicine & Bioinformatics (IPM&B), as a stand-alone virtual institute to deliver a model for genomic medicine within the District. This model would include both administrative and strategic objectives, with membership of the IPM&B allowing common interests to drive academic performance.

In March 2020, plans to formally launch the IPM&B were delayed by the arrival of, and responses to, COVID-19. So the IPM&B had an inauspicious entry but with strong support from Dr Teresa Anderson AM, Chief Executive and District senior executive, it has progressed. It aims to emulate the successes of similar stand-alone, discipline-specific bodies, such as the Institute of Academic Surgery and the Institute for Musculoskeletal Health.

3. Structure of the IPM&B

While functioning as a mini clinical stream, the IPM&B has two key objectives:

- strategic objective: to deliver innovative health care and research in genomics
- operational objective: to create an administrative and governance structure for health professionals working in genomics, funded by Sydney Local Health District but not aligned to a clinical stream.

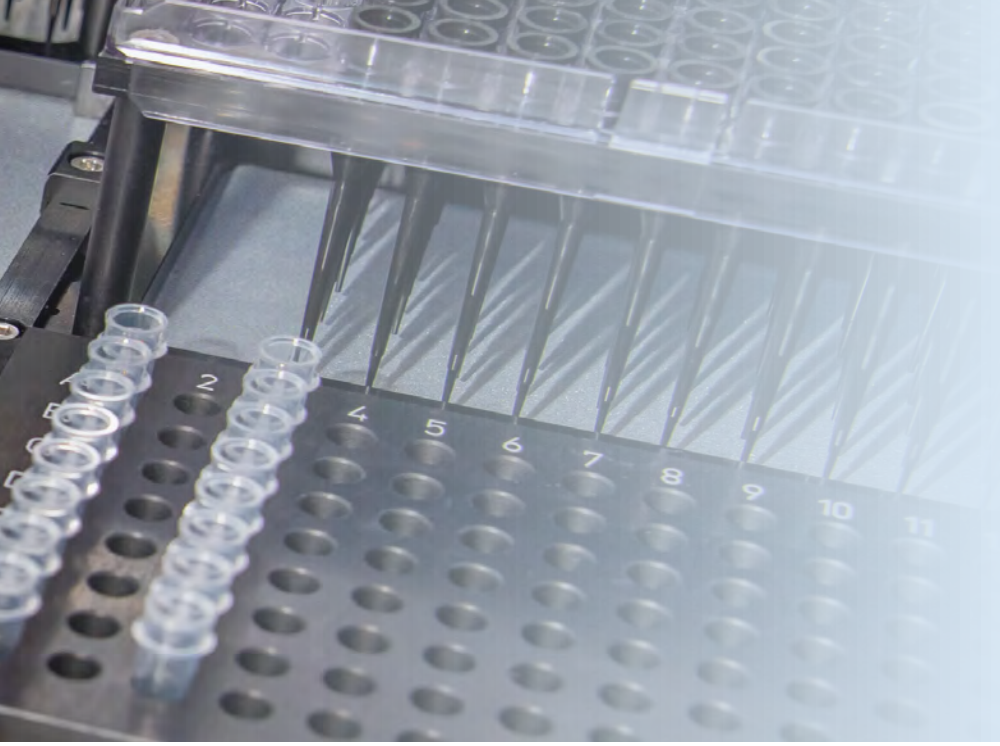
Therefore, a Strategic Organisational Chart and an Administrative Organisational Chart to reflect these activities are provided in Appendix I and Appendix II of this report.

The two organisational charts remain "work in progress"; particularly the strategic component as membership has grown quickly. This requires regular reviews of the diverse interest groupings to gauge how these are best engaged in precision medicine. In Section 11 – Initiatives, there is brief mention of metabolomics which illustrates the growing nature of precision medicine and the challenge how seemingly unrelated activities can be accommodated within a virtual institute. Overall, the current prime focus on genomics will be prioritised while allowing for other "omics" to be included. The common thread remains the health and well-being of patients and families in Sydney Local Health District and the broader NSW community.

The IPM&B's operational arm has been busy in 2020-21, particularly with COVID-19 activities making many of the administrative tasks more time consuming. It can be seen from Appendix II that there are now multiple categories of health professionals working in genomics and employed by Sydney Local Health District. They include the Clinical Genetics Service, a smaller team who are in the University of Sydney or NSW Health Pathology but work in somatic cell cancer services, a lonely bioinformatician (we hope that status is corrected in 2022), the first research nurse, and two Honorary Medical Officer clinicians.

Common to both organisational charts is the link of the IPM&B to senior executives within the two hospitals, the District Director of Research, and senior members in District Operations. The IPM&B Clinical Director reports to the District Chief Executive, Dr Teresa Anderson AM.

In 2022, the IPM&B Clinical Director will work to strengthen interactions with the General Managers at both RPA and CRGH.



4. Membership of the IPM&B

Health professionals

All health professionals with an interest in precision medicine are welcome to join the IPM&B (see Figure 1). Included in this very broad grouping are the many internal medicine disciplines and community genetics. This is only the start, and Professor Ron Trent, Clinical Director, was pleased to be asked by Dr David Eisinger to present to the urologists and trainees an overview of molecular biology in Urology: the first surgical group to "dip their toes" into the delights of genomics.

Building capacity in bioinformatics

As indicated earlier, the underlying theme in precision medicine is bioinformatics and how this capability will facilitate progress into genomics based clinical care and research. We started at the beginning of COVID-19 with a Bioinformatician (Ms Lauren Olafson) but then lost her as she moved to Perth for family reasons. So back to searching for another Bioinformatician and we were fortunate to appoint Dr Abdul Baten who was working in agricultural bioinformatics in New Zealand but previously had worked in Victoria, WA and most recently at Southern Cross University in NSW. Dr Baten and his family have now settled into life in Sydney and the IPM&B, and we are expecting, once he is appointed as an affiliate to the University of Sydney, that he will start growing genomics bioinformatics by training students in the clinical aspect of this discipline. A summary of work underway with Dr Baten is provided under Section 10 – Bioinformatics.

Community representation

The IPM&B was fortunate in 2021 to attract as its community representative Dr Alan McPhail. Dr McPhail is sought after by many of the key Sydney Local Health District clinical and research committees and has a vast understanding of the roles of community representatives in medicine. He is a valuable member of the IPM&B Executive Leadership Team (see Section 12 – Governance).

New Appointments in 2021

Two new appointments were announced in 2021. They are Professor Marina Kennerson from Concord's ANZAC Research Institute and Professor Clement Loy from the University of Sydney and Westmead Hospital. Marina is now a Deputy Director for the IPM&B and its Head of Research, while Clement is a Deputy Director of the IPM&B and its Head of Education. Both are outstanding academics and researchers with a strong commitment to training.

Figure 1: IPM&B membership

5. Clinical Genetics Service

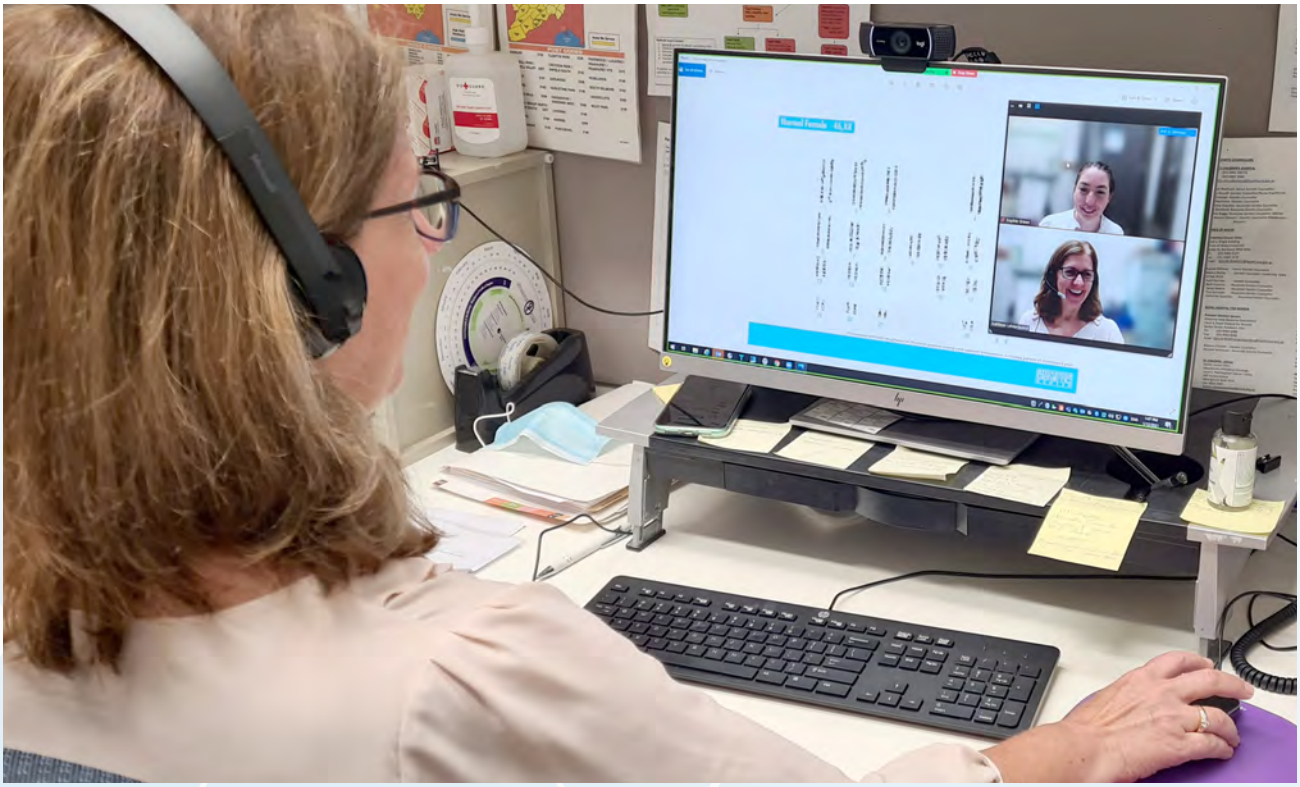
The Clinical Genetics Service at Royal Prince Alfred Hospital (RPA) is headed by Dr Lisa Worgan, Clinical Geneticist. In 2020 and 2021 she was supported by Dr Felicity Collins, Dr Lisa Ewans and Dr Amali Mallawaarachchi. Overall, there are 2.5 FTE Clinical Geneticists. In late 2021, the first Senior Genetic Counsellor in Sydney Local Health District, Kathleen Le Marquand, was appointed. Together with Ron Fleischer and Laura Molloy, the District now has 3.0 FTE Genetic Counsellors. Catherine Spinks, an Adult Metabolic Disorders Genetic Counsellor (1.0 FTE), works with the Department of Chemical Pathology. Administrative Support for the Clinical Genetics Service was provided by Panayiota Tsaglakis, Rita Pereira and a part-time database analyst.

In 2020, an important activity was the transfer of the Clinical Genetics Service staff from NSW Health Pathology to the IPM&B. This has allowed the Clinical Genetics Service to be integrated back into a clinical stream and the District's Division of Medicine for teaching, research and clinical care.

The team provide services in genetic assessment, counselling and testing for a wide range of outpatients, including neonatal, paediatric, adult and prenatal patients, in addition to inpatient consultations.

As many new treatments are being developed based on genomics, access to genetic services becomes increasingly important. The Clinical Genetics Service aims to provide the most up to date and inclusive genetic services for all patients in Sydney Local Health District.

Like all clinical services during COVID-19, the Clinical Genetics Service had to adapt quickly and now provides hybrid face-to-face and telehealth consultations.



Kathleen Le Marquand, Senior Genetic Counsellor, Clinical Genetics Service

The Sydney Local Health District Clinical Genetics Service is involved in many subspecialty multi-disciplinary clinics and aims to facilitate genetic diagnosis, genetic counselling, research and education. The team works closely with primary physicians to provide comprehensive genetic care to these complex patients. Strong and collaborative services have been established with multiple departments, as part of discipline specific services.

Figure 2: Clinical Genetics Service discipline specific services

6. Somatic Cell DNA Testing Service

Associate Professor Bing Yu, in collaboration with Professor Sandra O'Toole from the Tissue Pathology and Diagnostic Oncology Department at Royal Prince Alfred Hospital, set up a somatic cell DNA testing service in 2012. This was possible with Associate Professor Yu's background and laboratory expertise for designing DNA genetic tests for cancers such as melanoma, lung and colorectal. The service has grown rapidly and today there are 4.0 FTE Hospital Scientists assisting Associate Professor Yu; Spiridoula Kraitsek, Jie Qian, Jerry Wei and Cassandra Kavanagh (with the latter three funded by Sydney Local Health District). The service has an additional 1.0 FTE Technical Officer (Sidika Hallac).

Demand on somatic cell DNA testing continues to grow. The Royal Prince Alfred Hospital service is one of two in NSW Health Pathology providing a state-wide service for solid tumours. There is growing competition from private laboratories as the Medicare Benefits Schedule funds additional tests.

Reporting period	Melanoma	Non-small cell lung cancer	Colorectal cancer	Other	TOTAL samples
2017	438	287	175	48	948
2018	395	649	394	22	1460*
2019	468	600	326	13	1407*
2020	465	440	187	33	1125
Jan–Sept 2021	313	296	138	26	773

Table 1: Somatic Cell Cancer DNA Testing Service (Department of Medical Genomics laboratory, Royal Prince Alfred Hospital) – activity data 2017–2021

** The higher number of samples for 2018 and 2019 was due to the shift of all samples (over 600 per annum) from Hunter Molecular Genetics laboratory to Department of Medical Genomics laboratory RPA Hospital (RPA) (Hunter Molecular Genetics laboratory stopped performing these tests for 18 months during that period). The total number of tests from Department of Medical Genomics laboratory, RPA, is relatively stable with a slight increase per year.*

ctDNA in precision cancer

Associate Professor Yu works closely with the oncologists at the Chris O'Brien Lifehouse comprehensive cancer service. This has enabled him to consider the next developments in precision cancer, involving the testing of circulating tumour (ct) cells in patients with cancer. The ctDNA approach will value-add to precision medicine approach as it is non-invasive (it is sometimes called "liquid biopsy") and allows testing of tumours that might not be accessible to biopsy to supply a source of DNA. The ctDNA options include the monitoring for cancer recurrence after treatment, and should become a standard option in the model of care starting in 2022.

Pre-treatment stratification

- To determine therapeutic targets for cancer patients with a contraindication for invasive biopsy
- Alternative to insufficient tissue from core biopsy / fine needle aspiration
- Overall view of somatic mutations in primary and metastatic sites without sampling bias of tissue biopsy
- Characterisation of cancer genome (microsatellite instability, tumour mutation burden, genome scar, etc)

Therapeutic response

- Real time assessment of drug efficacy and treatment outcome
- Predict the durable clinical benefit for Immune checkpoint inhibition (ICI) patients

Monitoring

- Molecular residual disease (MRD) and recurrence
- Drug resistance and tumour evolution

Prognosis

- High risk of recurrence with delayed mutant clearance post-intervention

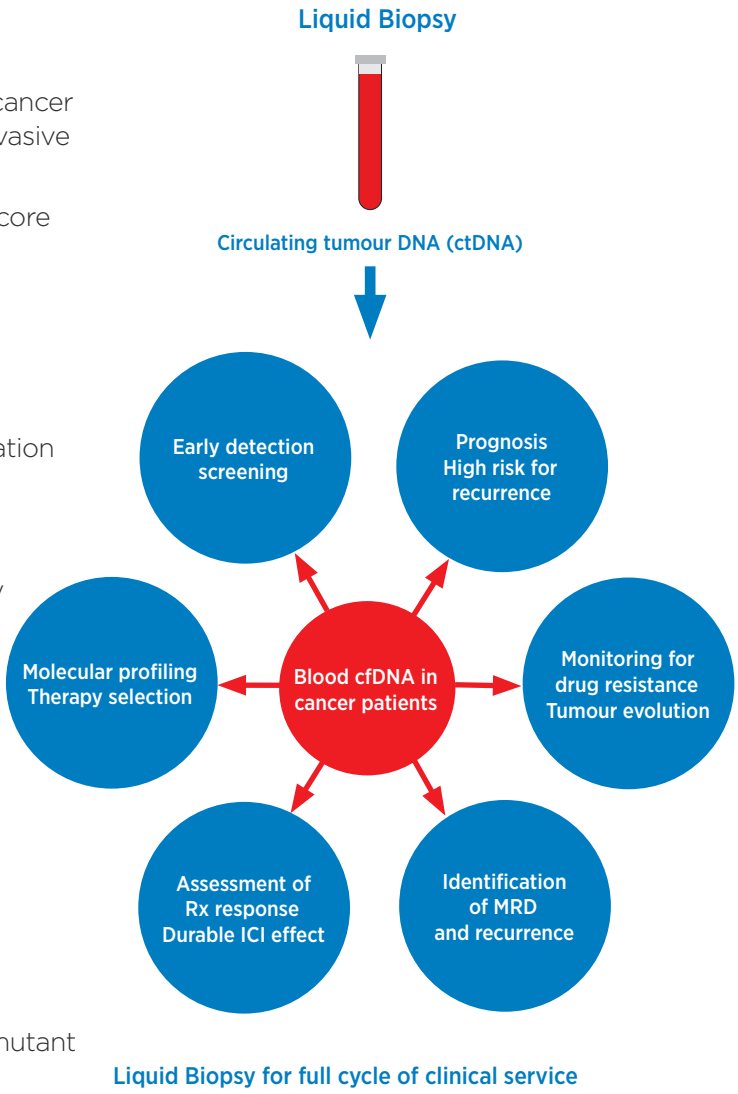


Figure 3: Liquid biopsy – clinical applications

7. Education and training

The first attempts at introducing the potential of genomics to a broader audience were undertaken in 2021 via the Genomics 2021 webinar series. The webinars were well received and the positive feedback will ensure these are a regular feature of the IPM&B educational activities moving forwards. They were recorded and so a library of educational material and resources is being developed.

The virtual webinar model was essential during the various restrictions and lockdowns with COVID-19 and the flexibility with timing and access was welcomed by participants. However, others noted the lack of interactions and networking. For 2022, a mix of virtual and face-to-face sessions will be arranged where possible.

Date	Presenter	Topic	Attendees
30 June 2021	Dr Anthony Cheong	DNA sequencing: today and tomorrow	57
28 July 2021	Professor Ron Trent	DNA variant classification: the ACMG criteria	49
25 August 2021	Dr Natasha Luquin	Pharmacogenomics: another strategy for precision medicine	41
29 September 2021	Dr Abdul Baten	Bioinformatics for genome analysis	47

Table 2: Genomics 2021 webinar series

Road to success in the MRFF funding scheme

During 2021, Professor Marina Kennerson, IPM&B Deputy Director and Head of Research, was awarded an MRFF genomics grant. This is a very competitive research funding scheme and we congratulate Professor Kennerson for bringing further prestige to the neurogenetics and genomics work coming from Concord Hospital and the ANZAC Research Institute. Professor Kennerson also presented a webinar where she illustrated her development as a basic clinical researcher and the types of collaborations and infrastructure development that allowed her to compete successfully with the best genomics researchers in Australia.

Genomics show-and-tell

In April 2021, between spikes of COVID-19 infections in NSW, we were able to present a face-to-face overview of genomics activities undertaken by impressive clinicians and researchers at Royal Prince Alfred Hospital (RPA). The purpose of this event was to attract the best of the advanced Fellow of Royal Australasian College of Physicians (FRACP) trainees to RPA, and encourage more to do higher degrees as part of their final years of training.

The program titled Showcasing genomic medicine in patient care and research: RPA experience was well received although, because of the disrupted timing of FRACP examinations with COVID-19, there were only a small number of trainees attending. In 2022, this educational activity will be repeated at a different date.

Speakers included:

Presenter	Topic
Professor Sebastiaan van Hal	SARS-CoV2
Dr Richard Bagnall	Using genomics to improve clinical care of people with inherited heart disease
Dr Amali Mallawaarachchi	Genomics in polycystic kidney disease
Dr Derek McCulloch	Molecular haematology: giemsa to genes
Professor Stephen Adelstein	Genomics in immunology
Associate Professor Bing Yu	Cancer genomics in solid tumours: precision oncology at the bedside

Virtual Annual Scientific Meeting

The first Annual Scientific Meeting for the IPM&B was held virtually in November 2021. The chosen theme, Functional Genomics, was timely as the rapid progress with DNA sequencing capability from panel-based to whole exome and whole genome has generated exponential data sets identifying many changes in DNA (both single base changes and structural variants). As expected, this produces a growing catalogue of DNA variants whose function, in relation to aetiology and pathogenesis, remains uncertain.

Speakers included:

Welcome address	**Dr Teresa Anderson AM** Chief Executive, Sydney Local Health District	
Session 1	**Chair: Dr Natasha Luquin** **Chief Scientist, IPM&B**	**Topic**
Keynote speaker	**Clinical Professor Bruce Bennetts** Molecular Genetics, The Children's Hospital Westmead	A journey from steam vents to a n=1
Keynote speaker	**Professor Marina Kennerson** Northcott Neuroscience Lab, ANZAC Research Institute; Head of Research, Deputy Director, IPM&B	Looking beyond the exome: navigating the structural variation genomic landscape of inherited peripheral neuropathies
Session 2	**Chair: Professor Clement Loy** **Head of Education, IPM&B**	**Topic**
Invited speaker	**Associate Professor John Kwok** Neurogenetics and Epigenetics Laboratory, Brain and Mind Centre	Challenges and progress in the functional genomics of neurodegenerative genes
Invited speaker	**Dr Ira Deveson** Genetic Technologies, Garvan Institute of Medical Research	Comprehensive genetic diagnosis of tandem repeat expansion disorders with programmable targeted nanopore sequencing
Concluding remarks	**Professor Ron Trent** Clinical Director, IPM&B	

8. Research

The focus of research and genomics from an IPM&B perspective during 2022 will be the potential for the IPM&B Head of Research (Professor Marina Kennerson) to work more closely with a small number of clinician researchers to encourage greater collaboration and interactions in preparation for opportunistic targeted calls for research funding opportunities.

The latter type of funding support has emerged as a growing activity with both government and non-government research organisations. As such there is often a short window for applications or expressions of interest. This is work in progress but is considered by the IPM&B executive as a worthwhile activity to pilot and, if successful, roll out a more comprehensive mentoring program.

Sydney Health Partners

In 2021, Sydney Health Partners, an organisation formed to assist research translation into evidence-based healthcare, called for expressions of interest for the formation of Clinical Academic Groups.
These would replace the previous streams and themes in Sydney Health Partners. The Clinical Academic Groups would be expected to deliver on four operational priorities:

- Supporting people
- Optimising innovation
- Enabling research
- Increasing impact.

The IPM&B considered the benefits of this initiative and an application was submitted. This was an important exercise for the IPM&B moving forwards, and immediately attracted as an external member of the IPM&B, Professor Carolyn Sue who is Executive Director of the Kolling Institute at the Royal North Shore Hospital. Carolyn is a leading Australian clinician-researcher in neurogenetics and there is considerable enthusiasm for the ongoing opportunities to work with her and the Kolling Institute.

35 applications for this initiative were received and 6 were successful. Unfortunately, the IPM&B's application was not successful. However, it was an important exercise to consider research priorities going forwards, and the leadership team for this IPM&B application was impressive. It is planned to continue an ongoing dialogue with this leadership team (Professor Clement Loy (Westmead Hospital); Professor Marina Kennerson (Concord Hospital); Associate Professor David Sullivan (Royal Prince Alfred Hospital); Professor Carolyn Sue (Kolling Institute); Associate Professor Devanshi Seth (Sydney Local Health District); Dr Natasha Luquin (Royal Prince Alfred Hospital); Dr Alan McPhail (IPM&B); Dr Abdul Baten (IPM&B) and Associate Professor Bing Yu (University of Sydney)).

Implementation science

Another benefit of applying for a Sydney Health Partner's Clinical Academic Group was the growing realisation that implementation science would, in future, comprise a core component of successful translational research grants. However, the understanding of this work (study of methods and strategies facilitating uptake of evidence-based practice and research into clinical care and policy) remained rudimentary. Fortunately, Professor Clement Loy, IPM&B's Head of Education, had previously taught a unit of study in implementation science for a University of Sydney Masters program. He agreed to include this topic as part of the IPM&B's ongoing educational activities.

9. Communication

e-Newsletter

As a profile building strategy for the IPM&B, a monthly e-Newsletter is produced by Melissa Cole, IPM&B Operations Manager. Each e-Newsletter features a clinician/researcher profile or particular precision medicine/genomics activity. The subscriber list for the e-Newsletter has steadily grown since the IPM&B's establishment, with each issue now reaching over 130 health practitioners with an interest in precision medicine, both within Sydney Local Health District and externally. Copies of the 2021 eNewsletters are included in Appendix V. This communication strategy will continue in 2022.

Webinar series survey

Following the Genomics 2021 webinar series, a survey of attendees was undertaken to gather feedback. The survey response rate was 22 per cent and very positive feedback was received both in terms of overall ratings for the webinars and also particular aspects such as the level of information delivered and whether attendees gained new knowledge through the sessions. Attendees who responded provided suggestions for improvement, such as the need to be able to network and have more open discussion through these forums, and also future webinar topics which we can use to inform our decisions around the next series. Full survey results are included in Appendix IV.

The survey provided a boost to the IPM&B subscriber list with 60 per cent of respondents signing up to receive the monthly e-Newsletter and 100 per cent of respondents requesting notifications of future IPM&B webinars.

Intranet

The IPM&B has an informative intranet site through which we promote news and upcoming events. During 2021 we have built a library of educational genomics recordings via the webinar series and Annual Scientific Meeting, the links to which are available through the intranet site. Unfortunately access is restricted to Sydney Local Health District staff which limits applicability.

In order to foster collaborations and networks, the IPM&B will need to engage with a greater number of externally based health professionals and researchers moving forward. An externally available internet site will be key to expanding the promotion of the IPM&B's activities in education, research and training.

Social media

During 2021, the IPM&B established a small presence on social media via Twitter and LinkedIn accounts. Apart from the e-Newsletter, these channels are important as we seek collaborations with health professionals external to Sydney Local Health District.

10. Bioinformatics

A goal for many years at Sydney Local Health District (the District) was to appoint a Bioinformatician to allow the growing needs for genomics to be met. Comparable infrastructure is available clinically as ICT (Information Communication Technology) services have grown to enable the traditional paper forms to give way to electronic means for patient records, delivering medications, laboratory reports and various modes of communication. The same changes have occurred in genomics with the large data sets generated requiring:

- sophisticated genomics analysis pipelines; and
- storage facilities.

Both are no longer able to be provided through local server capabilities, and progress to cloud computing is now gaining rapid momentum.

In changing technology environments, the input from a Bioinformatician becomes essential. Looking ahead, the applications of artificial intelligence and machine learning to decision making algorithms in genomics makes it more critical to have bioinformatics capability.

For many years the significance of bioinformatics has been appreciated but the availability of this expertise has been limited. Therefore, increasing capacity remains a key function of the District's Genomics Bioinformatician.

Sydney Local Health District leads the way in embedding bioinformatics expertise in clinical services, with the appointment of Genomics Bioinformatician, Dr Abdul Baten.

Dr Baten (pictured) has had a broad background in bioinformatics and will fit in nicely with the many activities requiring his input.

The following table provides some insight into the many tasks he has taken, despite constraints from COVID-19 in 2021.

2021 Work activities in genomics bioinformatics

Activity	Summary	Collaborator
Molecular haematology report generation in leukaemia	Various bioinformatics pipelines are needed to identify somatic variants and further analysis is required to curate/annotate those variants. This enables an automatic report generation pipeline. This pipeline is implemented with python programming language. The pipeline is designed with an easy-to-use graphical user interface (GUI) and binary executables which allows the program to run in any windows platform without the need for a python programming environment and dependent libraries.	Prof Harry Iland
Somatic cell cancer service	Numerous activities including: gene coverage from BEDGRAPH data; Archer hooks for data backup; qPCR and ctDNA data analyses; comparisons of MiSeq and NextSeq coverage; storage genomic data.	A/Prof Bing Yu and colleagues
Genomics analysis pipeline	Participation in various discussion and planning around a pipeline for the state-wide genomics analysis. Various programs evaluated, and organised training session with service providers, for example, Alissa, Sophia genetics etc). Also, met and discussed with colleagues from other hospitals (for example, CRGH, Randwick Genetics) regarding the pipelines they use and their benefits and limitations.	NSW Health Pathology
Nanopore technology	Design, implementation and testing of a pipeline to identify SNVs and large structural variations using Nanopore long read data. This is a large-scale ongoing project, and some preliminary results are being generated.	Dr Anthony Cheong and Dr Hugh French
Cloud computing and storage	Working to design, test and deploy cloud-based computing and storage facilities. As we urgently need high performance computing environments for large-scale bioinformatics analysis (for example, Nanopore long-read project), we are working with Sydney Local Health District ICT for proof-of-concept cloud infrastructure.	Mitchell Burger, Sydney Local Health District ICT Services
Alternative Splicing	This is a collaborative project to explore the patterns of intron retention alternative splicing events in lymphoma patients. SNVs are identified from the whole genome sequencing data and the objective is to identify recurring SNPs around splice sites that could explain aberrant splicing in those patients.	Prof John Rasko and A/Prof Ulf Schmitz, Centenary Institute

Networking and bioinformatics

A requirement, prior to appointment as the Genomics Bioinformatician for Sydney Local Health District (the District), was for Dr Baten to interact with clinicians, researchers and bioinformaticians across the District campus and the adjacent University of Sydney. This has worked well with the following activities undertaken in 2021:

- presented at Grand rounds at Royal Prince Alfred Hospital (RPA) with Professor Ron Trent
- presented three bioinformatics seminars to the Department of Medical Genomics, RPA
- contributed a three part “Bioinformatics” 101 e-Series
- participated in all the IPM&B meetings and seminars
- delivered a webinar in the IPM&B Genomics 2021 webinar series
- visited scientists at Concord Hospital to discuss projects including bioinformatic aspects
- met with various researchers at RPA, University of Sydney, Centenary Institute
- met with District and NSW Health Pathology bioinformaticians to collaborate on projects.

11. Initiatives

During 2020-21 work commenced on a number of IPM&B initiatives.

Pharmacogenomics

Pharmacogenomics is a growing discipline within precision medicine. It utilises genomics testing to determine the genetic capability of an individual to metabolise drugs administered for therapeutic purposes. A proportion of the population, because of genetic changes in the drug metabolising genes, are less likely to respond to these drugs in the standard doses (reducing the drug's efficacy) or will have an exaggerated response to the drug (leading to high risk of serious adverse events (SAEs)).

Pharmacogenomics has both therapeutic and preventive applications:

- Enhancing the efficacy of drug by identifying those who need higher drug doses to achieve the same therapeutic benefits, and, at the other end of the spectrum
- Identifying those who need lower doses or must avoid the drug to reduce the risk of SAEs.

There is currently no comprehensive pharmacogenomics service available through NSW Health Pathology. There is only one private NSW laboratory with this capability which is available on a user pay mechanism as there is no Medicare Benefits Schedule item available. The IPM&B has sufficient clinical expertise and, in partnership with NSW Health Pathology, has the analytic platforms and laboratory expertise to establish a comprehensive pharmacogenomics service at Royal Prince Alfred Hospital.

Pharmacogenomics will benefit a number of clinical areas including Psychiatry, Oncology, Rheumatology, Transplant, immunology, Cardiology and Geriatrics. Collaboration with Sydney Local Health District pharmacists is crucial to the service and the University of Sydney's School of Pharmacy has expressed interest in partnering with the District on this project.

Metabolomics in clinical care

Metabolomics and other omics such as proteomics, lipidomics and transcriptomics exemplify technologies with the potential to drive precision medicine into the future. Metabolites are small molecular chemical entities (biomarkers) involved in metabolism. A collection of all metabolites is called the metabolome. Metabolomics and the other "omics" share with genomics a fundamental reliance on data management and bioinformatics capabilities that are accessible through the IPM&B.

Professor David Sullivan, a senior member of the IPM&B, has proposed the development of a memorandum of understanding with medical research laboratories involved in biomarker production. Those markers that show promise in preliminary work could be moved along the translational pipeline into routine clinical use as high throughput NATA validated assays. This partnership between the research laboratories, the Department of Chemical Pathology, with the assistance of the IPM&B, could offer "user pays" expansion of biomarkers underpinned by the clinical expertise of the clinician researchers who best understand the pathophysiology.

An early example of this capability is the measurement of α-keto-δ-($N^G N^G$-dimethylguanidino)-valeric acid (DMGV) as an early marker of insulin resistance and future risk of non-alcoholic fatty liver disease, diabetes and cardiovascular disease. Beyond genomics, other categories of molecular analysis dubbed with the "omics" suffix are providing diverse insights into pathophysiology. The IPM&B will assist in this translational research proposal by providing:

- advice in bioinformatics
- infrastructure and administrative support
- promotion via educational activities such as monthly e-Newsletter and presentations on metabolomics.

Neurogenomics

Professor Clement Loy was appointed in 2021 as an Honorary Medical Officer within the IPM&B. He is a neurologist, with a long and impressive track record in clinical research. He is the head of the Huntington disease service at the Westmead Hospital, and a Professor at the University of Sydney. His attachment to Sydney Local Health District is timely as it comes with the recent appointment to Concord Hospital (CRGH) of Professor Steve Vucic, an internationally recognised expert in neurodegenerative disorders. The clinical neurology team now building at CRGH is impressive, and with further collaborations including the previous reference to Professor Carolyn Sue, neurogeneticist at the Kolling Institute, will contribute to the clinical and research work already underway with Professor Marina Kennerson, Professor Garth Nichsolson and Dr Kishore Kumar.

Dr Anthony Cheong was appointed at the beginning of 2021 to take on a District-funded genetic pathologist position which allows him to work at both CRGH (Department of Molecular Medicine) and Royal Prince Alfred Hospital (RPA) (Department of Medical Genomics). This will integrate nicely into the developments described above and, in the longer term, will allow both District DNA genetic testing laboratories to work closer together and have a higher impact in relation to their contributions to the Statewide NSW genomics services located within NSW Health Pathology. With his training in the Weatherall Institute of Molecular Medicine in Oxford as a background, Dr Cheong has started to consider the clinical applications of third generation sequencing, a technology which allows long reads to be used to detect a greater range of DNA rearrangements that can lead to genetic disease. In this work he is partnering with our enthusiastic genetic pathology trainee in the Department of Medical Genomics at RPA (Dr Hugh French) and will work with experts in the Garvan Institute of Medical Research.

External collaborations

The Garvan Institute of Medical Research is strategically aligned with the University of NSW but has always interacted with many of the clinicians at RPA and CRGH. Professor Chris Goodnow, the Executive Director at the Garvan, has encouraged many of these informal ad hoc collaborations. During 2021 work has started to develop a more formal memorandum of understanding between the District and the Garvan to further expand and strengthen collaborations. This is work in progress.

12. Governance

Just as in Section 3 of this report, mention was made that the strategic structure of the IPM&B continues to evolve, so will the governance structure as membership grows and the focus of the IPM&B broadens. It is noteworthy that currently all key leadership positions (except for the consumer representative) are held by clinicians. This will need review as the interests associated with precision medicine are expanded.

Management Committee

Although called "Management Committee", this group functions more as an advisory committee. The Committee meets quarterly and its membership is listed below. Terms of Reference for the Management Committee are found in Appendix III. As the IPM&B grows it might be more appropriate to consider a formal Board structure taking on the management role and an expanded Management committee taking on the important advisory and strategic functions. This will be work in progress.

Professor Ron Trent	Director, IPM&B. Chair of committee
Professor Marina Kennerson	ANZAC Research Institute, CRGH; Deputy Director, IPM&B
Professor Clement Loy	Westmead Hospital, USYD; Deputy Director, IPM&B
Melissa Cole	Operations Manager, IPM&B; Secretary of committee
Dr Natasha Luquin	Chief Scientist, IPM&B (WHS, QA)
Dr Anthony Cheong	Genetic pathology, SLHD
Professor David Sullivan	Chemical pathology, RPA
Professor Harry Iland	Molecular haematology, RPA
Associate Professor Roger Garsia	Associate Dean, USYD
Associate Professor Vivien Chen	Haematology, CRGH
Dr Lisa Worgan	Clinical Genetics Service, SLHD
Dr Margaret Janu	Laboratory services, CRGH
Associate Professor Stephen Adelstein	Immunology, RPA
Dr Kishore Kumar	Neurogenetics, CRGH
Dr Elizabeth Robertson	Cardiologist, external members
Professor Tim Lambert	Psychiatry, CRGH
Professor Warwick Britton	Director of Research, SLHD
Professor Sebastiaan van Hal	Molecular microbiology, RPA
Dr Abdul Baten	Bioinformatician, SLHD
Associate Professor Susan McLennan	NSW Health Pathology*
Dr Alan McPhail	Consumer Representative

**The relationship between the IPM&B and NSW Health Pathology is an important one but also evolving. This will benefit from more work in 2022*

Executive Leadership Team

This group meets monthly and has expanded during 2021 as new appointments were made. Presently the Executive Leadership Team includes: Professor Ron Trent (Chair), Melissa Cole (Secretary), Dr Natasha Luquin (QA and Chief Scientist), Dr Alan McPhail (Consumer Representative), Professor Clement Loy (Deputy Director, Head of Education) and Professor Marina Kennerson (Deputy Director, Head of Research). Input from this group has been invaluable to progress various initiatives and activities of the IPM&B.

13. Finance

2020-2021 Financial year

The IPM&B cost centre (cc 454728) finished the 2020-2021 financial year with a $101K surplus. A breakdown of key figures is provided below.

	FY 2020/2021 Year Total		
	Actual	Budget	Var
Expenses			
Employee related	1,843,397	1,806,588	(36,809) U
Goods & Services	(21,936)	24	21,960 F
Repairs, Maintenance & Renewals	2,070	-	(2,070) U
TOTAL EXPENSES	**1,823,531**	**1,806,612**	**(16,919) U**
Retained Revenue	(96,546)	(19,334)	77,212 F
NET COST OF SERVICES	**1,726,985**	**1,787,278**	**60,293 F**
Government contributions	(40,793)	-	40,793 F
RESULT FOR THE YEAR	**1,686,193**	**1,787,278**	**101,085 F**

2021-2022 Financial year

October 2021 year-to-date figures for cc 454728 are provided below. A request for a budget enhancement has been submitted to address the deficit in employee related costs.

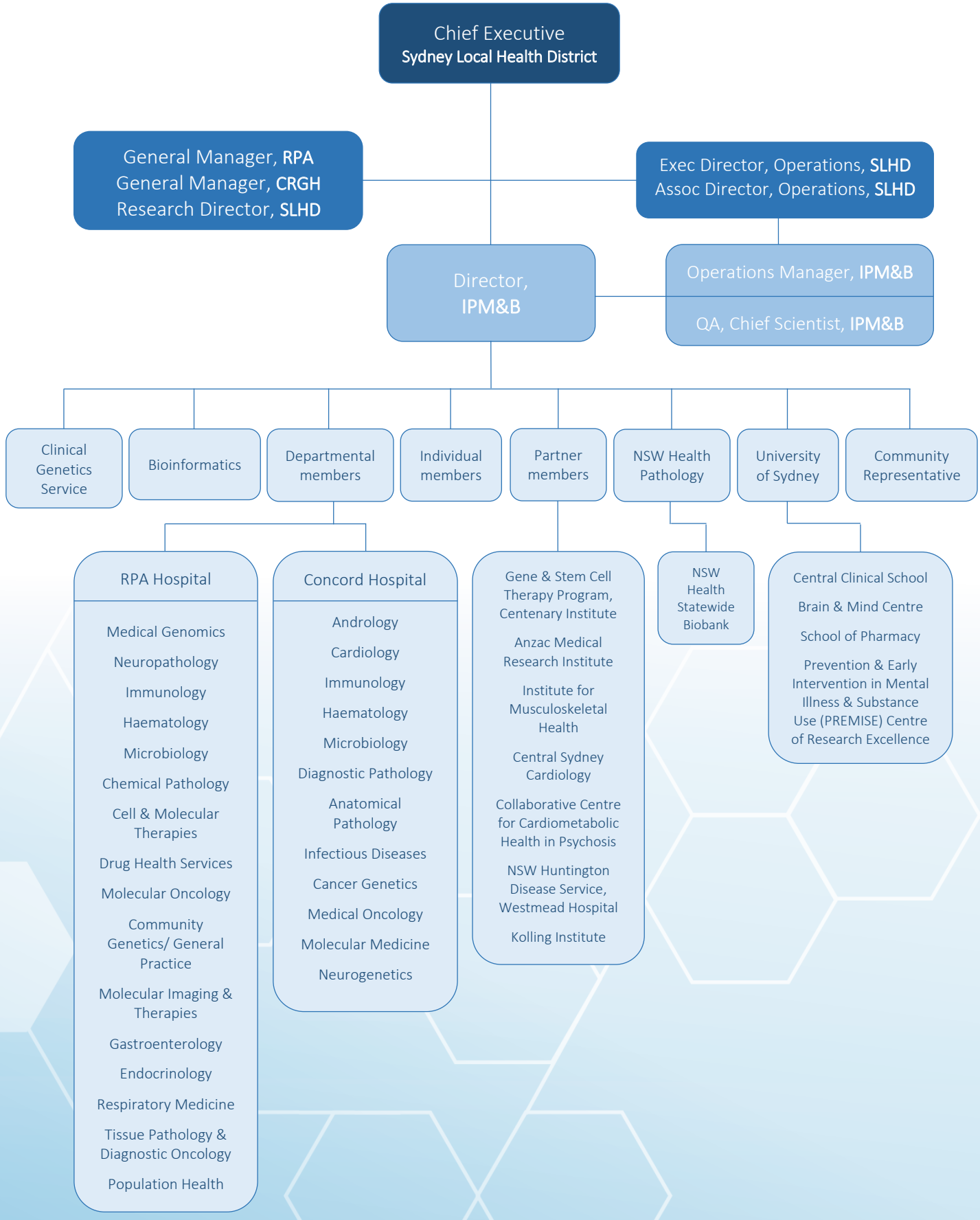
	FY 2021/2022 October		
	YTD_Actual	YTD_Budget	Var
Expenses			
Employee related	791,078	612,579	(178,499) U
Goods & Services	(13,494)	112,819	126,313 F
Repairs, Maintenance & Renewals	147	12,558	12,411 F
TOTAL EXPENSES	**777,731**	**737,956**	**(39,775) U**
Retained Revenue	(21,168)	(31,536)	(10,368) U
NET COST OF SERVICES	**756,563**	**706,420**	**(50,143) U**
Government contributions	(22,678)	-	22,678 F
RESULT FOR THE YEAR	**733,885**	**706,420**	**(27,465) U**

The majority of the IPM&B's activities are recorded in cc 454728. The reliance on a single cost centre is problematic because of the varied activities and groups involved. In 2022 it will be necessary to break down the cost centre into different ones reflecting work and activity undertaken.

The IPM&B also has a cost centre for external donations.

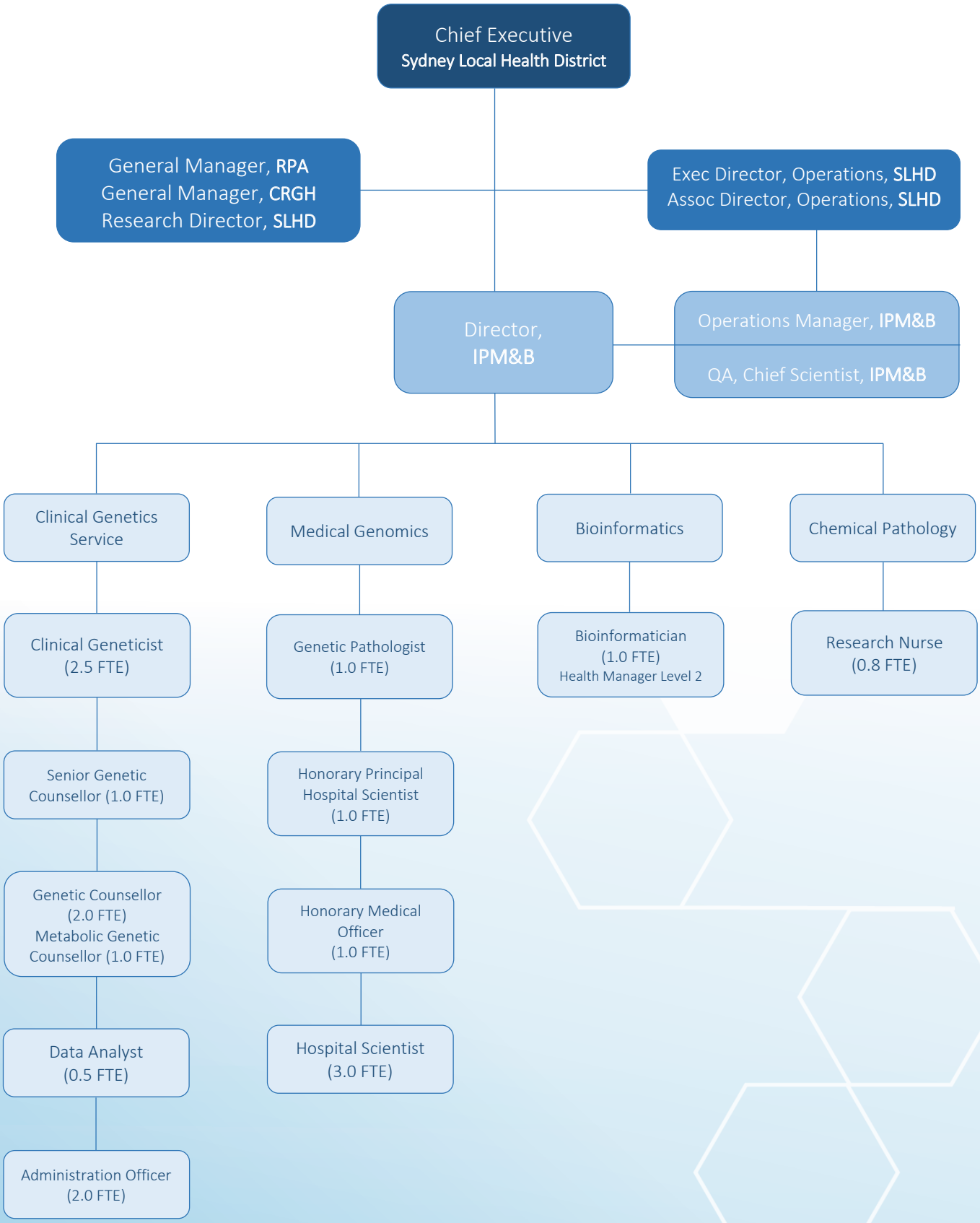
Appendix I

IPM&B Strategic Organisational Chart



Appendix II

IPM&B Administrative Organisational Chart



Appendix III

Terms of Reference for IPM&B Management Committee

Terms of Reference for Management Committee

Version 15 July 2020

- The Management Committee will advise the Director on strategic directions for the IPM&B and other matters brought to this Committee. The Director may call on experts within the IPM&B to assist him/her on particular issues.
- The Management Committee will meet four times per year. In circumstances where immediate advice is required, the Director may call an extraordinary meeting of the Management Committee. This may be an electronic meeting.
- Membership of the Management Committee will comprise:
    - One or more representative(s) of each Department (or corresponding facility) that is a Departmental Member of the IPM&B
    - One or more representative(s) for the Individual Members in the IPM&B
    - One representative from NSW Health Pathology
    - IPM&B Bioinformatician or nominee
    - One representative from the Clinical Genetics Service
    - Associate Dean or nominee of the Central Clinical School, Faculty of Medicine and Health, University of Sydney
    - IPM&B Chief Scientist / WHS Officer or nominee
    - Community representative.

From the above committee members an IPM&B Head of Research and an IPM&B Head of Education will be elected.

- The IPM&B Director (or nominee) will chair the Management Committee meetings, and the Secretary for the Management Committee will be the IPM&B Operations Manager (or nominee).
- The Management Committee will take responsibility for organising the Annual Scientific Meeting of the IPM&B. The Operations Manager will assist in this work.
- The Terms of Reference for the Management Committee will be reviewed annually.

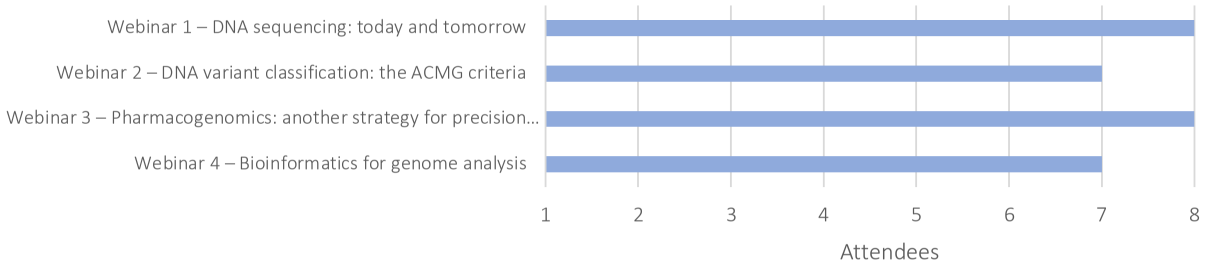
Sydney Local Health District

Institute of Precision Medicine

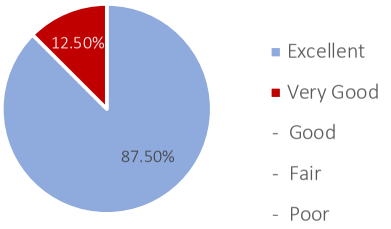
GENOMICS 2021 WEBINAR SERIES

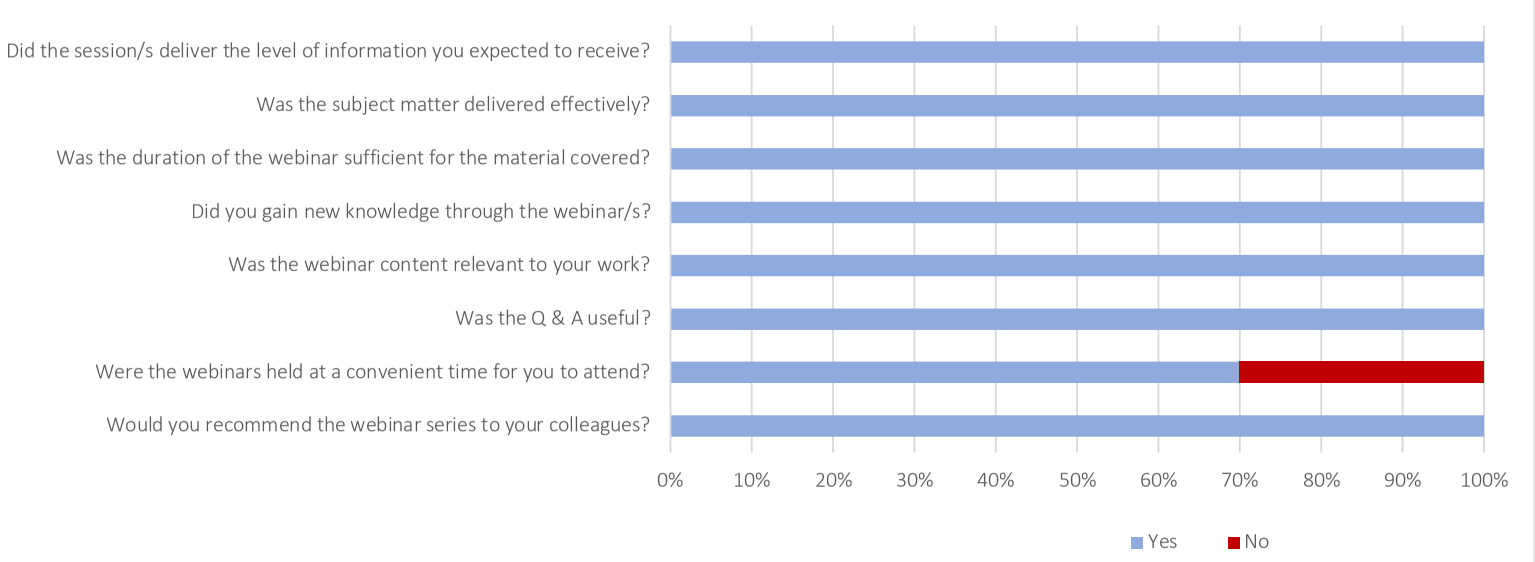
Attendee survey results

Which webinars did survey respondents attend?



Overall rating for webinar/s attended





Genomics 2021 Webinar Series – Survey results (cont)

Did we meet your expectations?

- Yes, absolutely.
- Yes, it was fantastic to listen in to.
- The content was perhaps more complex for me in relation to prior knowledge and application to my work, but I still learned new things from the talk. (Webinar 3)
- Excellent bioinformatics talk.

Suggestions for improvement

- None; organisation was flawless and the sessions were moderated very efficiently.
- Excellent topics and I was able to view recordings for Webinar 2 and 4. Prefer sessions to be on either Monday or Friday, but as long as they are recorded that is fine. Thanks for organising the webinars.
- The webinar format is very passive. There is minimal interaction within the audience as a whole. Might be better to have as seminar so it is more interactive. It is important for the audience to be able to network through this forum. Webinar format restricts that.

Suggestions for future webinar topics

- More on bioinformatics, more on big data storage.
- Impact of genomics in future medicine.
- From the specialty groups in the hospital – I am biased, but I would love to share the work we are doing in neuropathology.
- Cancer NGS.
- Why not run some 'Translational' seminars showing an actual usage case where a complex case is 'solved' and embedded in same is a pivotal role for genomics. Similarly you could do a theoretical – but commonplace – scenario. There could be an outline of the problem and how genomics could clarify ambiguities that can't easily be resolved clinically.
- Laboratory procedures: cell culture, selection and processing for whole cell-based genetic analysis; nucleic acid preparation, storage and labelling, PCR, and methylation analysis.

Follow up

- 80% of survey respondents requested links to IPM&B Webinar session recordings
- 100% of survey respondents requested notifications regarding future IPM&B Webinars
- 60% of survey respondents subscribed to receive the IPM&B e-Newsletter monthly bulletin

Appendix V IPM&B e-Newsletter – 2021 issues

Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 24 FEBRUARY 2021

Pharmacogenomics and Precision Medicine

IPM&B Chief Scientist, Dr Natasha Luquin

Pharmacogenomics is the relationship between genetic variants and their effect on an individual's response to a drug. An example of precision medicine, the clinician has access to a patient's genetic profile to guide the selection of the right drug, at a dose that is optimally therapeutic and avoid severe side effects. For example, the presence or absence of certain genetic variants can determine the degree to which the related drug is metabolised (classified as poor, intermediate, normal, rapid or ultrarapid metabolisers). By determining the patient's metabolism status for that particular drug, the prescribing clinician can determine whether the drug dose needs to be altered or an alternative drug administered to prevent ineffective treatment or an adverse drug reaction (sometimes life-threatening immune-mediated toxicity or myelosuppression).

Avoiding these adverse drug reactions not only benefits the patient but also provides an economic saving to the health system. It has been reported that adverse drug events contribute 2-4% of all adverse events, with an average cost of $14,027 per adverse drug event (PMID 16768660). Further, poor patient response can reduce a patient's quality of life and thus increase their use of healthcare resources. A recently published Australian study found that of the 5,408 patients genotyped for the CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes, approximately 96% patients had at least one actionable pharmacogenetic variant (PMID 30191366).

Actionable gene variants have been identified in genes that code for cytochrome P450 drug metabolising enzymes (CYP genes), drug transporters (eg, *SLCO1B1*) and the human leukocyte antigen B proteins (*HLA-B*). The therapeutic areas impacted by pharmacogenomics include: cardiology, neurology, anaesthesiology, psychiatry, gastroenterology, rheumatology, immunology, malignant disease and immunosuppression. Currently, there are only two pharmacogenetic tests subsidised by the MBS: *HLA-B*-abacavir in the treatment of HIV and *TPMT*-thiopurines.

One of the main barriers to clinical implementation of pharmacogenomics is the translation of the genetic results to that which is actionable in clinical practice. There are now 25 evidence-based clinical dosing guidelines published for over 30 drug-gene pairs by the Clinical Pharmacogenetics Implementation Consortium (CPIC; Web link). These dosing guidelines help clinicians understand how the pharmacogenetic results should be interpreted to optimise drug therapy.

Dr Natasha Luquin
BSc(Hons) PhD
Chief Scientist, IPM&B

TPMT/NUDT15 and thiopurine-induced toxicity

The Dept of Medical Genomics (RPAH) introduced Thiopurine S-Methyl-transferase (TPMT) genotyping in 2011 to guide thiopurine dosing. TPMT, an enzyme that metabolises thiopurine drugs such as azathioprine and 6-mercaptopurine, is used in the management of chronic inflammatory conditions (such as Crohn's disease, rheumatoid arthritis), acute lymphoblastic leukaemia and organ transplantation. The absence or reduction of TPMT enzyme activity increases the risk of thiopurine-induced toxicity, which includes life-threatening myelosuppression, due to the excess accumulation of active metabolites.

*In 2019, the CPIC updated their genotype-based dosing guidelines for thiopurine, adding nudix hydrolase 15 (NUDT15) genotyping to the TPMT genetic test (PMID 30447069). In response to this international recommendation, the RPA laboratory has now added a NUDT15 variant (NUDT15*3 and *2) to the existing TPMT assay. A retrospective study that genotyped NUDT15*3 in patients that had previously tested negative for TPMT only, identified ten patients with the NUDT15*3 variant. Three of these patients had exhibited signs of thiopurine toxicity. Two patients required hospitalisation when administered azathioprine therapy, both for pancytopenia and one with life-threatening anaemia. The third patient was not hospitalised but azathioprine therapy was ceased due to abnormal liver function tests. These cases highlight the importance of pharmacogenetic testing and the need to provide a comprehensive pharmacogenetics service in line with international dosing guidelines.*

Pre-emptive pharmacogenomic testing: Paradigm for preventive medicine

Pharmacogenetic testing in Australia primarily uses a reactive testing approach, ie genetic testing of a single gene at the time of prescribing a drug. The disadvantages of this approach are that treatment may be delayed or a drug inappropriately prescribed, whilst the treating clinician awaits the genetic test result. Pre-emptive pharmacogenomic testing, where a patient is screened for a large number of genes before it is known what particular drug is to be prescribed, means that the patient's genetic information is already available at the disposal of the clinician as a new drug treatment is required throughout the patient's life. This adds a preventive medicine component to some treatments.

Advances in genetic testing allow for many pharmacogenetic genes to be tested simultaneously. Further, as strong evidence for new drug-gene pairs emerge, gene panels can be expanded to incorporate this information (as shown by the TPMT/NUDT15 example above). Pre-emptive pharmacogenomic testing is a more cost-effective testing approach than multiple single-gene tests.

For more information, see the following link for the article by the Australian Journal of General Practice: Pharmacogenomics in general practice: The time has come. Also see the Royal College of Pathologists of Australasia's (RCPA) position statement on pharmacogenomics: Utilisation of pharmacogenetics in healthcare.

From our Director

We welcome Dr Abdul Baten to the role of Genomics Bioinformatician for the IPM&B. Dr Baten has over 10 years' experience providing high-quality bioinformatics research support and solutions to a wide range of projects. Look out for Dr Baten's Bioinformatics 101 series launching with our next issue.

Prof Ron Trent

NSW GOVERNMENT Health Sydney Local Health District

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www.slhd-intranet.sswahs.nsw.gov.au/slhd/ipmb.html

Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 24 MARCH 2021

From our Bioinformatician

Dr Abdul Baten, BSc, PhD

I am excited to join the Institute of Precision Medicine & Bioinformatics as Genomics Bioinformatician.

Bioinformatics is already playing a key role in the IPM&B and the past year has seen several important and successful collaborations with various groups at RPAH and SLHD. I am keen to continue that legacy along with teaching, training and outreach initiatives.

First, I would like to take this opportunity to give a short introduction to my Bioinformatics background and experiences. My Bioinformatics journey started in 2005 when I started my PhD at The University of Melbourne. Human genome sequencing was just completed and there was a vast amount of genomics data that required computational methods to analyse those data.

Computational identification of genes was an important area of research, and accurate identification of splice sites was a key component of successful gene finding methods. In my PhD, I developed algorithms to identify splice sites accurately in the human genomes using machine learning methods. The principal was to train my splice site detection method using a small dataset of known splice sites and use that trained model to identify splice sites in human genomic DNA data. In my thesis, I also analysed splice sites in the context of alternative splicing mechanisms, ie exploring the properties of constitutive and alternative splice sites.

I started my post-doctoral research at the Harry Perkins Medical Research Institute at The University of Western Australia. My core responsibilities included analysing genomic and transcriptomic data generated from various disease-related projects, particularly large-scale type-1 and type-2 diabetes projects. I also explored the pathways and key genes involved in the pancreatic beta-cell differentiation project utilising transcriptomic data and differential gene expression at various developmental stages.

I moved to Southern Cross University in Lismore, NSW at the end of 2012 with an opportunity to inaugurate their first Bioinformatics lab.

I initiated Bioinformatics research, training, teaching as well as setting up the core Bioinformatics infrastructure at SCU. My major focus was plant genomics and I've led several genomes and transcriptome sequencing projects that had national significance, including Macadamia, Corymbia and Brassica rapa genome sequencing projects. Also, as a co-investigator, I completed several metagenomics and marine genomics projects. I supervised several Masters and PhD students and taught an undergraduate Bioinformatics unit in the Department of Health and Human Science as the unit assessor. In 2018, I took an opportunity to gain valuable industry experience in a similar role with AgResearch, New Zealand. AgResearch is a New Zealand Government scientific research institute where I served until taking up my current role.

Although Bioinformaticians sit well behind the frontline in a clinical environment, increasingly they are more integrated with the patient-care pathway and play a critical role in the analysis of data and interpretation of results. I am interested in applying my knowledge and skills to understand molecular mechanisms, diagnosis, and potential therapies for human diseases.

At the IPM&B, I have already initiated several interesting projects and look forward to working with you in the future. Please do not hesitate to contact me regarding any aspects of Bioinformatics.

Dr Abdul Baten, BSc, PhD
Genomics Bioinformatician, IPM&B
abdul.baten@health.nsw.gov.au
Ph 02 9515 5079

IPM&B's first symposium: Showcasing genomic medicine in patient care & research

As part of our education initiative, the IPM&B is pleased to present our first symposium – *Showcasing Genomic Medicine in Patient Care and Research: RPAH Experience* – on Thursday 22 April 2021 at the CPC Auditorium, with registration from 5:00pm and guest speakers 5:30-7:00pm.

Featuring talks from six eminent clinicians and researchers, the symposium will highlight the impressive genomic activities at RPAH and the opportunities for inclusion of genomics into clinical training and research. See following for the full program and guest speaker details.

Connect with us now on Twitter at @SLHD_IPMB

NSW GOVERNMENT Health Sydney Local Health District

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics
E-NEWSLETTER 19 APRIL 2021

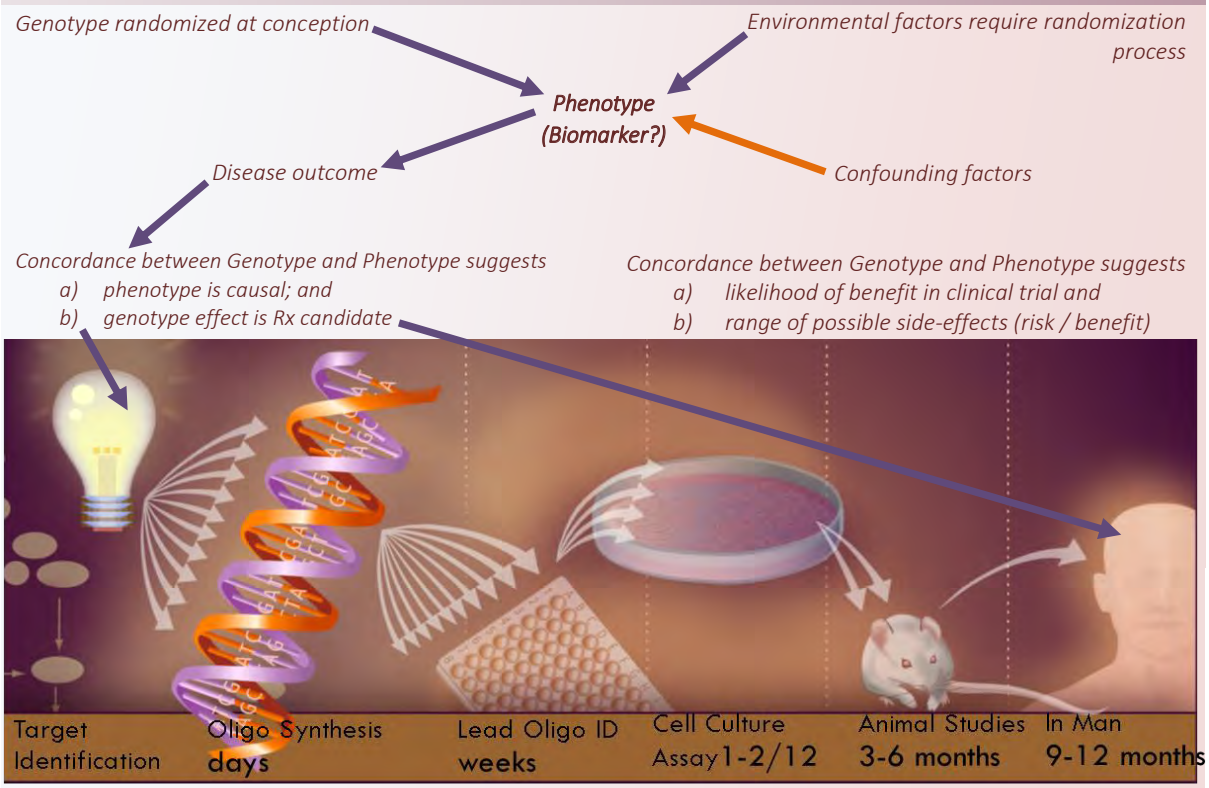
Mendelian Randomization uses Bioinformatics to design Precision Medicines

Prof David Sullivan, Dept of Chemical Pathology, RPAH

The Department of Chemical Pathology within the Institute of Precision Medicine & Bioinformatics at RPAH has past and on-going experience with successful novel therapies based on the principle of Mendelian Randomization, which is sometimes referred to as "Nature's Clinical Trial". This technique allows inferences about causality to be made from observational studies because it prospectively controls for confounding influences and reverse causality. In retrospect, it affirmed the safety and efficacy of statin therapy. It also provided real-time assurance supporting the safety and efficacy of cholesterol absorption inhibitors whilst discouraging the continued development of drugs which increase protective HDL cholesterol by inhibiting cholesterol ester transfer protein. It identified Proprotein Convertase Subtilin Kexin-9 (PCSK9) as a safe and effective target for next generation cholesterol-lowering therapy and in doing so, led to the evolution of a new paradigm for the design and development of therapeutic innovations, illustrated by the agent "Incliseran". This new paradigm, which relies on the design of antisense oligonucleotides or related agents, has led to highly effective treatments for aortic stenosis, athero-thrombotic cardiovascular disease (CVD) and massive hypertriglyceridaemia. Our department has been involved with all these enterprises and is currently undertaking outcome trials targeting apolipoprotein (a), apolipoprotein C3 and ANGPTL3 to prevent coronary artery disease and recurrent pancreatitis.

Mendelian Randomization is based on the perfectly unbiased randomization of alleles that exert modest effects on phenotypic traits when they segregate at conception. The life-long effects of the resultant differences in phenotype are extremely powerful. For example, loss of function PCSK9 variants reduce LDL cholesterol by about 30%, which in turn reduces CVD risk by 90%. The guiding principle of Mendelian Randomization is as follows: if the genotype and phenotype exert the same effect on the disease in question,

Mendelian randomization at work



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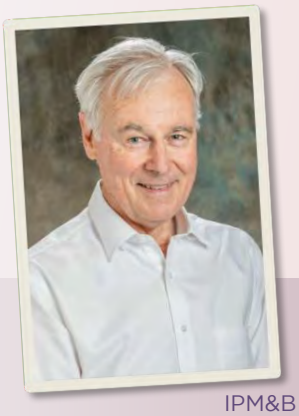
that phenotype is likely to be causative of the disease and treatments aimed at the gene's mechanism of action are likely to be effective. The phenotype is also informative about the possibility of side-effects associated with such treatments. For example, homozygous PCSK9 loss-of-function patients and PCSK9 knock-out mice exhibit very low cholesterol levels but remain completely healthy in all respects.

This has led to an approach in which favourable findings regarding outcome, together with reassuring findings regarding safety, raise the prospects of positive results from randomized controlled trials to reduce the target in question, as was the case with anti-PCSK9 therapy in the Fourier trial. The sequence from the target gene is known, so candidate siRNAs can be designed very rapidly. Selected candidates can progress to in vitro and in vivo testing in an accelerated fashion and in-human studies can commence much sooner than has been the case in the past. This, together with the previously mentioned anticipation of clinical outcomes and side-effects, has enabled product development to be substantially accelerated with greater prospects for success.

Mendelian Randomization can be performed on publicly available data sets. It is largely based on GWAS and other data in repositories, such as the UK Biobank. Findings may be influenced by the ethnic mix of the population concerned, so there are grounds for the development of similar repositories in Australia. At the moment, most of clinical trials (and the accompanying intellectual property) is flowing back into the hands of multinational private companies.

The most essential component for the conduct of Mendelian Randomization assessments is expertise in bioinformatics, which is necessary to access, interface and analyse the separate components of the data. The IPM&B is actively pursuing this imperative, as illustrated by the recent appointment of Dr Abdul Baten as the Institute's Genomics Bioinformatician.



Prof David Sullivan
MB BS, FRACP, FRCPA
Clinical Associate Professor
Dept of Chemical Pathology, RPAH

See following for our new Bioinformatics 101 e-Series from Dr Abdul Baten, IPM&B Genomics Bioinformatician

Don't miss the IPM&B Showcase on Genomics this week

The IPM&B's first Showcase will be held this Thursday from 5pm at the Susan Wakil Health Building. Featuring talks from six eminent clinicians and researchers, the Showcase will highlight the impressive genomic activities at RPAH. Registration for this free event is by email to SLHD-IPM&B@health.nsw.gov.au

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics

Showcasing genomic medicine in patient care & research: RPAH experience

Highlighting opportunities for inclusion of genomics into clinical training & research at RPAH

PROGRAM

Thursday 22 April 2021

Susan Wakil Health Building Level 4, Rm 416

5:00–5:30pm	Registration and welcome
5:30–5:45pm	Molecular virology Prof Sebastiaan van Hal Senior Staff Specialist, Infectious Diseases & Microbiology, RPAH
5:45–6:00pm	Using genomics to improve clinical care of patients with inherited heart disease Dr Richard Bagnall Head, Bioinformatics & Molecular Genetics Lab, Centenary Institute
6:00–6:15pm	Genomics in polycystic kidney disease Dr Amali Mallawaarachchi Staff Specialist, Clinical Geneticist & Nephrologist, Clinical Genetics Service, IPM&B
6:15–6:30pm	Molecular haematology Dr Derek McCulloch Staff Specialist, Institute of Haematology, RPAH
6:30–6:45pm	Genomics in immunology A/Prof Stephen Adelstein Head, Dept of Immunology, RPAH
6:45–7:00pm	Cancer genomics in solid tumours A/Prof Bing Yu Head, Somatic Cell DNA Testing Service, Dept of Medical Genomics, RPAH

FREE EVENT REGISTRATION by email to SLHD-IPM&B@health.nsw.gov.au

NSW GOVERNMENT Health
Sydney Local Health District

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics
E-NEWSLETTER 20 MAY 2021

Extracts from the IPM&B Showcase
Genomic medicine in patient care & research: RPAH experience

The IPM&B showcase held on 22 April was a successful evening with our guest speakers providing examples of how their work in genomics has transformed clinical care, research or led to novel models of care. The presentations highlighted ways in which genomics can enhance training at RPAH and also identify research opportunities.

Special thanks to our guest speakers for giving their time to this initiative. Abstracts from the Showcase are reproduced with permission below.

Molecular Virology

Prof Sebastiaan van Hal
Senior Staff Specialist
Dept of Infectious Diseases & Microbiology, RPAH

The spread of SARS CoV2 from Hubei province in China led to a global pandemic. This event led to rapid changes in our approaches to viral diagnosis including the use of molecular methods such as Whole Genome Sequencing (WGS). The evolution of the virus resulted in the emergence of variants with increased infectivity and transmissibility. Treating and management decision of these patients required quicker turn-around times and led to the transition of WGS into a diagnostic laboratory workflow. The modern virology and microbiology laboratory is now a workplace with an intense focus on genomic technology to enable clinical decision making from the bedside, with acutely ill patients, to the community where asymptomatic patients have the potential to open up new hot spots of infection. Although the current focus is on COVID-19, the knowledge gained will prove invaluable with the next epidemic or pandemic. Much has been learnt in a very short time frame with new models of care based entirely on the rapid generation of genomic data using third generation sequencing technologies for WGS before this same approach has been rolled out in the more traditional genetic specialties.

Genomics in Immunology

A/Prof Stephen Adelstein
Head, Department of Clinical Immunology and Allergy, RPAH

Genome research has provided clinicians and scientists with a catalogue of all known human genes, knowledge of their location and structure, and an ever-growing list of variants in DNA sequences found among individuals in different populations. The advent of whole genome sequencing has started to realise the potential for integration of this information into clinical practice. Changes in the genetic sequences of populations and individuals can then account for the clinical phenotypes of disease. This is especially evident in Immunology where there are now more than 500 mutations described in genes that code for proteins that perform a variety of functions of the intact human immune response and correlate with known disease expression, especially in the inherited immunodeficiencies.

The findings have lead not only to a greater understanding of normal immune function but also to the real possibility of treatment by both gene therapies and the development of new therapeutics or repurposing of existing drugs to counter the defects exposed by the genetic mutations. More recently perturbation of somatic gene function leading to a variety of more common clinical presentations have been described that raises further exciting possibilities for research and treatment.

These advances and their roles in clinical practice in the diagnosis and management of immunological diseases will be reviewed in two cases that illustrate the role of genomics in diagnosis and treatment in Clinical Immunology.

Connect with us now on Twitter at @SLHD_IPMB

Genomics in Polycystic Kidney Disease

Dr Amali Mallawaarachchi
Clinical Geneticist & Nephrologist
Clinical Genetics Service, IPM&B

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenic cause of kidney disease, with a prevalence of 1 in 1000. The condition is associated with significant morbidity and accounts for ten per cent of end stage kidney disease in Australia. ADPKD is largely caused by disease-causing variants in the PKD1 or PKD2 genes. Largely due to significant technical challenges in sequencing the PKD1 gene, genetic diagnostics has previously been only infrequently offered to families with ADPKD. Through genomics research performed at the Garvan Institute, in conjunction with RPAH, we have developed a world-first, more robust sequencing method for ADPKD, utilising whole genome sequencing (WGS). In subsequent work, we showed that performing genomic sequencing in patients with clinical features of polycystic kidney disease has utility in defining the cause of disease, particularly in patients with atypical clinical features. These research findings have helped to guide clinical practice in ADPKD, particularly in defining which patients are most likely to benefit from genomic investigation.

There are numerous opportunities to participate in kidney genomics research at SLHD, including ongoing studies investigating somatic mutation in patients with ADPKD, identifying new mutational mechanisms in ADPKD patients with genetically undiagnosed disease and in identifying genetic causes of disease in patients with kidney failure of unknown cause.

Using genomics to improve clinical care of patients with inherited heart disease

Dr Richard Bagnall
Head, Bioinformatics & Molecular Genetics Laboratory
Centenary Institute

The inherited heart diseases are a collection of heart muscle diseases and abnormal heart rhythm disorders. Inherited heart diseases are autosomal dominant conditions; thus, first-degree relatives have a 1:2 chance of inheriting the causal genetic variant. Finding the precise genetic cause of disease with cardiac genetic testing is an important step in clinical management of our patients and their family members as this immediately translates into improved clinical care. We have shown that cardiac genetic testing can clarify an uncertain clinical diagnosis, which may alter clinical management of patients. Cascade genetic testing of first-degree family members can release gene-negative relatives from needless, ongoing, clinical screening. Postmortem-genetic testing is an important addition to the investigation of the causes of sudden cardiac death in the young and can identify additional causes of death. We use functional genomics assays to help clarify the clinical relevance of variants and thus increase the genetic testing diagnostic yield. Most recently, we are leading the Australian Genomics Cardiovascular Genetic Diseases Flagship to build evidence to embed cardiac genetic testing into mainstream, population-based, national health care.

Molecular Haematology

Dr Derek McCulloch
Staff Specialist
Molecular Haematology Laboratory
Institute of Haematology, RPAH

The care of patients with malignant blood cancers relies on the accurate sub classification from a wide variety of disease types. Increasingly, the accurate diagnosis, disease prognostication and targeted management of blood cancers relies on the ability to identify the molecular lesions within the tumour. Indeed within the 80 World Health Organization (WHO)-defined myeloid neoplasms and acute leukaemias certain cancers are clearly defined by their driving mutations, for example Acute Promyelocytic Leukaemia (APL) with PML-RARA.

Early identification of the gene fusion in patients with APL allows the use of entirely novel chemotherapy-free in some patients with leukaemia-free survival >95%. Some molecular aberrations become genetic tumour markers whose rate of disappearance correlates with treatment response, predicts the chances of survival and can be used to identify very early disease relapse, months before symptoms would appear.

The exciting future for Acute Myeloid Leukaemia treatment will involve the use of next generation sequencing to identify the molecular mutations present at diagnosis, and use that knowledge to design bespoke anti-leukaemia therapy for each patient. Through molecular monitoring of so-called minimal residual disease, disease relapse and the evolution of new mutations will be detected and, the therapy can co-evolve to give better disease control. In haematology, registrars are already developing their genomic language skills, utilizing their knowledge to improve patient care and researching better detection and treatment of blood cancer.

Cancer genomics in solid tumours – Precision oncology at the bedside

A/Prof Bing Yu
Head, Somatic Cell
DNA Testing Service
Dept of Medical Genomics, RPAH

Cancer is a genetic disorder resulting from the accumulation of mutations in oncogenes and tumour suppressor genes. Susceptible mutations can be inherited in 5-10% familial cancers. Most cancers result from the acquisition of mutations during cell division or exposure to carcinogens. Such acquired/somatic changes are only present in the tumour cells. Understanding of cancer genomics has initiated a paradigm shift from conventional cancer medicine towards a precision oncology model of care.

In lung cancer, detection of somatic DNA mutations in EGFR, ALK and ROS1 has enabled successful target therapies and improved the survival of patients. At the genome level, high tumour mutation burden and high microsatellite instability predict an enhanced sensitivity to immune checkpoint blockage in several solid tumours.

Homologous recombination deficiency score can be obtained based on loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions. This score is an independent predictor for responsiveness to the poly (ADP-ribose) polymerase inhibitors. Tumour heterogeneity and dynamic changes are unique to the cancer genome. Real time genomic information retrieved from blood circulating tumour DNA (ctDNA) can guide precision-based management in solid tumours. Compared to tissue biopsies, a blood collection is less invasive and allows repeated sampling. This makes ctDNA appealing in:

(i) The detection of somatic mutations,
(ii) Assessment of therapeutic response,
(iii) Monitoring of minimal residual disease and relapse,
(iv) Identification of drug resistance, and
(v) Prognosis.

Potential issues of ctDNA in clinical applications will be discussed. Further research is required before ctDNA analysis can deliver its promises and advance the next phase in precision oncology.

See following for the next issue in our new Bioinformatics e-Series from Dr Abdul Baten, IPM&B Genomics Bioinformatician

Have you registered for our 2021 lunch time Webinar Series?

The IPM&B is hosting a series of lunch time webinars in 2021 with topics ranging from DNA sequencing and Variant classification to Pharmacogenomics and Bioinformatics for genome analysis. Full details below.
Register by email to SLHD-IPM&B@health.nsw.gov.au

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics

WEBINAR SERIES: Genomics 2021

We welcome you to join our webinar series:

Webinar 1 DNA sequencing: today and tomorrow

Dr Anthony Cheong

This webinar will provide a background on sequencing technologies used today & the emerging technologies that will become clinically relevant in the future

Wednesday | 30 June | 1–2pm

Webinar 3 Pharmacogenomics: another strategy for precision medicine

Dr Natasha Luquin

An introduction to the application and implementation of pharmacogenomics to improve drug safety and efficacy

Wednesday | 25 August | 1–2pm

Webinar 2 DNA variant classification: the ACMG criteria

Prof Ron Trent

Making sense out of DNA changes detected in DNA genomic sequencing – which ones are the mutant disease-causing changes?

Wednesday | 28 July | 1–2pm

Webinar 4 Bioinformatics for genome analysis

Dr Abdul Baten

How bioinformatics is used for the analysis of large data sets generated by next generation sequencing

Wednesday | 29 September | 1–2pm

REGISTER by email to SLHD-IPM&B@health.nsw.gov.au

NSW GOVERNMENT Health
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Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 21 JUNE 2021

Diagnosis by Social Media

Dr Anthony Cheong
Staff Specialist
Genetic Pathologist
IPM&B, SLHD

Diagnosis by social media is often discouraged. However it can prove to be handy sometimes.

Dr Alice Grey, Immunology Fellow at RPAH, follows medical journals on social media. An occasional glimpse on a post last year caught her eye – a newly described syndrome called VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic). It is characterised by a late adulthood onset, often fatal, treatment-refractory inflammatory disorder with fevers, cytopenias, characteristic vacuoles in myeloid and erythroid precursor cells, dysplastic bone marrow, neutrophilic cutaneous and pulmonary inflammation, chondritis and vasculitis.

These apparently non-related signs originate from mutations in UBA1, a gene coding for the major E1 enzyme that initiates ubiquitylation. Ubiquitylation is a cellular process whereby misfolded proteins are tagged for degradation. The UBA1 gene is found in chromosome X, so males are more likely to be affected than females. The mutation is somatic, meaning only cells from certain tissues have the mutation and in this case, they are cells from the myeloid lineages.

The signs described in the publication were very much similar to a patient of Dr Grey – an older gentleman with multi-system inflammatory disorder without a diagnosis over the last 3 years. Trials of various medications were unsuccessful, and he also subsequently developed myelodysplastic syndrome. This was a light bulb moment – an assay was quickly set up in the Medical Genomics laboratory to look for an UBA1 mutation. With help from the Haematology Department cells from the myeloid and lymphoid lineages were also separated by FACS (flow-assisted cell sorting). An UBA1 p.Met41Thr mutation was confirmed in two days, within a month of publication on VEXAS syndrome. A great team effort across three different disciplines!

References

Beck, D.B., Ferrada, M.A., Sikora, K.A. et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. New Engl J Med (2020); 383:2628-2638.

Grey, A., Cheong, P.L., Lee, F.J. et al. A Case of VEXAS Syndrome Complicated by Hemophagocytic Lymphohistiocytosis. J Clin Immunol (2021).

Future Directions for IPM&B

It is just over 12 months since the establishment of the IPM&B and there are some important genomics initiatives underway which I will summarise in a future e-Newsletter. Presently, there are two interesting projects under consideration and of potential interest to IPM&B members who may want to join these activities, or provide advice.

The first is in **Metabolomics** with Prof David Sullivan (Head of Chemical Pathology, RPAH), the lead investigator to consider how promising biomarkers might be translated into clinical care through high throughput validated assays using mass spectrometry technology. The second project is around **Pharmacogenomics** with Dr Natasha Luquin (IPM&B and Medical Genomics) working with Prof Tim Lambert (Psychiatry, Concord Clinical School) and NSW Health Pathology to develop a clinical grade pharmacogenomics panel also using mass spectrometry technology. Email SLHD-IPM&B@health.nsw.gov.au if you'd like more information about these activities.

Prof Ron Trent

Have you registered for our Genomics 2021 Webinar Series?

Webinar 1 DNA sequencing: today and tomorrow

Our Webinar series kicks off next week with Dr Anthony Cheong discussing sequencing technologies that are used today and the emerging technologies that will become clinically relevant in the future.

Wednesday 30 June 1–2pm

Register by email to SLHD-IPM&B@health.nsw.gov.au

Connect with us now on Twitter at @SLHD_IPMB

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Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 21 JULY 2021

Introducing IPM&B Deputy Directors

In this e-Newsletter we are introducing two dedicated and talented members of the IPM&B: Prof Marina Kennerson, who has been appointed as Head of Research within the IPM&B, and a Deputy Director. Also Prof Clement Loy, who will take on the role of Head of Education and Deputy Director. I welcome Marina and Clement to these roles in the IPM&B.

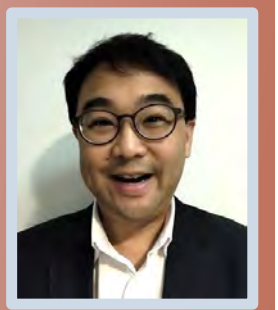
I have worked with Clement for many years in the Westmead Huntington disease program of which he is the Director, with the RPAH Medical Genomics Department providing the DNA genetic testing. Clement demonstrates impressive teaching, research and administrative skills and is a dedicated and caring clinician managing patients with Huntington disease and their families. Marina is a very committed researcher in neurogenetics and neurobiology. I have followed her work which now has come together with the recent award of a prestigious Australian MRFF grant. For the past year both have generously given their time to assist with development of the IPM&B, and no doubt will make outstanding contributions in the near future. Prof Ron Trent

Head of Research, Deputy Director IPM&B Professor Marina Kennerson

Dr Marina Kennerson is a Professor of Neurogenetics/ Neurosciences with the ANZAC Research Institute and Sydney Medical School, University of Sydney. Marina received her Bachelor of Science (Hons) degree from University of New South Wales and MSc (Med) and PhD from the University of Sydney. Her scientific training included mapping genes for inherited neurodegenerative diseases and using genomic technologies to identify causative gene mutations. Through her training Marina was introduced to inherited neuropathies (Charcot-Marie-Tooth (CMT) neuropathy) and motor neuron disorders and she has continued to contribute to this field of research for over 25 years. Through the Gene Discovery and Translational Genomics Program she heads, Marina's team have discovered several neuropathy genes and are doing pioneering research to investigate the role of structural variation mutations causing gene dysregulation. Her program uses numerous "omics" technologies as well as induced pluripotent stem cell (iPSC) derived motor neurons and in vivo systems (C. elegans and mouse) to model mutations for pre-clinical studies. Marina is the Scientific Director of the Asian Oceanic Inherited Neuropathy Consortium (AOINC), a board member of the International Charcot-Marie-Tooth and Related Neuropathies Consortium (CMTR) and serves on the Scientific Advisory Board for the US based CMT Research Foundation. As a researcher, she is passionate about disseminating CMT and rare neurogenetic disease awareness, making her research collaborative and accessible to the wider research and lay community as well as advocating for young career scientists and students who are the heart and soul of her research team and program.

As the newly appointed Head of Research at the IPM&B, Marina brings a wealth of research experience that can help guide collaborative and productive research activities. The cornerstone to these activities will be encouraging "multiomics" approaches as a central theme for the IPM&B that will leverage the expertise within SLHD for diagnosing disease, investigating disease mechanisms, and translating this into clinical care.

Head of Education, Deputy Director IPM&B Professor Clement Loy



Clement Loy is a cognitive neurologist with subspecialty training at the Dementia Research Centre, National Hospital for Neurology and Neurosurgery, Queen Square, London; and laboratory training in molecular genetics at the Garvan and Prince of Wales Medical Research Institutes. He is a Professor at the Brain and Mind Centre, the University of Sydney; and Director and Neurologist at the Huntington Disease Service at Westmead. He has a longstanding interest in the genetic forms of dementia, having provided care for families with familial Frontotemporal Dementia, familial Alzheimer Disease, and Huntington Disease, in London and Sydney, since 2003. He has summarised his approach to the familial dementias in a Lancet review. Clement's current research interests include gene-silencing trials for people with Huntington Disease, and design of clinical

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trials for pre-manifest expansion carriers using a genotype-based enrichment/ precision medicine approach. He serves the wider community as a member of the Pharmaceutical Benefits Advisory Committee.

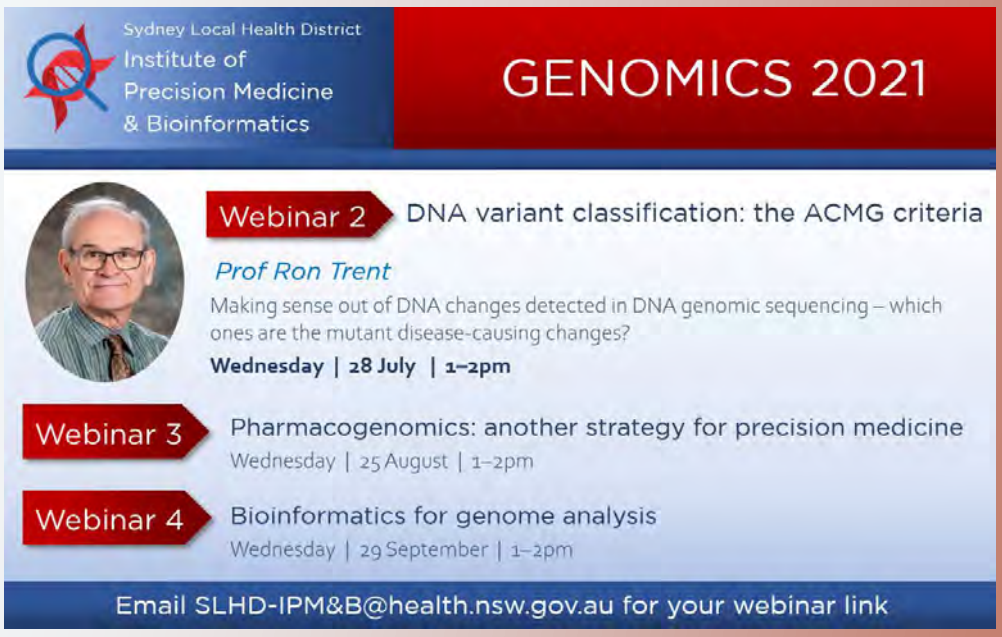
The IPM&B has brought together expert clinicians, scientists and researchers from a broad spectrum of disciplines, and is the ideal forum for cross-disciplinary learning. As Head of Education, Clement looks forward to learning from, and facilitating cross-disciplinary learning among our Institute members.

Through the integration of laboratory, bioinformatic and clinical activities, together we will be able to translate genetic technology to personalised diagnosis, prognosis, treatment – and ultimately, better patient outcomes.

IPM&B 2021 Webinars

Thanks to all those who tuned in for Dr Anthony Cheong's webinar last month "DNA sequencing: today and tomorrow". Our Genomics 2021 Webinar Series continues next week with Prof Ron Trent discussing "DNA variant classification: the ACMG criteria". Email SLHD-IPM&B@health.nsw.gov.au for your webinar link.

We are also pleased to be presenting "My journey to a MRFF" – a webinar with Prof Marina Kennerson discussing the successful MRFF grant she has just been awarded. With Q & A included, this will be a valuable session for those interested in applying for a MRFF grant soon or in the future. Details below.



Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 17 AUGUST 2021

Bioinformatics and Cloud computing in genomic medicine

The appointment earlier this year by SLHD of a genomics bioinformatician and, from this, the building of capacity in bioinformatics, is starting to pay dividends.

Recently, NSW Health has indicated that there will be a move from local computer servers (associated with high costs to purchase and then upkeep), to Cloud-based computing. This will benefit the implementation of genomic medicine as significant computing power is needed to analyse the very large and complex data sets (gigabytes to terabytes in size) generated through genomics DNA sequencing. Flowing from this is the requirement to store rapidly growing data sets.

The move to Cloud computing is underway through NSW Health Pathology, and SLHD has started to work with that organisation to enable access to Cloud computing for analysis and storage of genomic data for researchers and clinicians at RPA and Concord hospitals. In this work, the IPM&B is being assisted by SLHD Director of Strategy, Architecture, Innovation and Research, Mr Mitchell Burger and his ICT team, and from the IPM&B there is Dr Anthony Cheong (Genetic Pathologist) and Dr Abdul Baten (Genomics Bioinformatician) who are working with members of the Department of Medical Genomics (A/Prof Bing Yu and Dr Hugh French), Department of Haematology (Prof Harry Iland) and Department of Microbiology (Prof Sebastiaan van Hal).

The first goal is to utilise Cloud computing to improve the analysis of genomics data. A/Prof Yu, who leads the somatic cell cancer DNA testing team, now reports he can analyse, with access to Cloud computing, a large number of genomic tests within 2.5 hours which represents a vast improvement over the time taken with conventional computers. This will reduce the turnaround time allowing patients' results to be obtained earlier.

The second goal involves working with NSW Health Pathology to build storage capacity and access the analytic power of that organisation's Cloud. These capabilities are required to develop the future genomics analysis pipeline at SLHD.

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See following for the next issue of our Bioinformatics 101 e-Series, with Dr Abdul Baten discussing the impact that long-read sequencing (sometimes called 3rd generation sequencing) will have on genomics for research and clinical care. Much has happened since 1978 when Fred Sanger in Cambridge described his enzyme-based DNA sequencing approach (called 1st generation sequencing) which contributed to genomics for >30 years, and only recently is being overtaken by 2nd generation sequencing characterised by the generation of many millions of short reads generated in parallel and then assembled through bioinformatics "muscle".

Prof Ron Trent

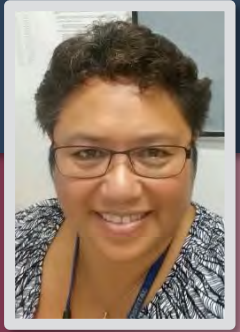
Haematology (CRGH): New publication

Building platelet phenotypes: diaphanous-related formin 1 (DIAPH1)-related disorder

David Rabbolini, Hai Po Helena Liang, Marie-Christine Morel-Kopp, David Connor, Shane Whittaker, Scott Dunkley, Dea Donikian, Mayuko Kondo, Walter Chen, William S Stevenson, Heather Campbell, Joanne Joseph, Christopher Ward, Timothy Brighton, **Vivien M Chen**.

PMID: 34223798 DOI: 10.1080/09537104.2021.1937593

Upcoming IPM&B Webinars

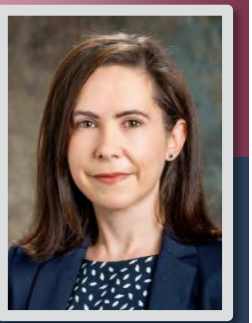


My journey to a MRFF

Prof Marina Kennerson

Wednesday | 18 August | 1–2pm

Email SLHD-IPM&B@health.nsw.gov.au for your webinar link



Pharmacogenomics: another strategy for precision medicine

Dr Natasha Luquin

Wednesday | 25 August | 1–2pm

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics
E-NEWSLETTER 17 SEPTEMBER 2021

Liquid biopsies: Profiling cancer mutations without invasive tumour biopsies

A/Prof Bing Yu
Head, Somatic Cell DNA Testing Service
Dept of Medical Genomics, RPAH

Cancer is a genomic disorder caused by the accumulation of mutations in DNA. Non-inherited (acquired) mutations in cancer are called somatic mutations. They are present in more than 90% of solid tumours and result from errors during cell division or exposure to an oncogenic environment such as smoking or ultraviolet radiation.

Mutation profiling in solid tumours is now a core component of precision oncology by providing critical information for treatment selection, diagnosis and prognosis. For example, EGFR activating mutations indicate the increased sensitivity to tyrosine kinase inhibitors in non-small cell lung cancer, while mutations in the RAS and BRAF genes suggest lack of response to anti-EGFR antibody-based therapies. Solid tumours keep evolving in their mutational profile with some emerging mutations producing resistance to therapy that was previously effective.

Somatic mutations involved in oncogenesis are only present in tumour cells. Therefore, tissue biopsy is required to obtain tumour DNA. However, every biopsy is a snapshot of a specific site at a particular stage in cancer progression. Within this snapshot, sampling bias can provide misleading information due of tumour heterogenicity in the primary tumour and/or its metastases. Endoscopic biopsies take time to arrange and, at times, are contraindicated due to poor health, potential cancer seeding/dissemination, or bleeding risk. Even a successful tissue biopsy may not produce sufficient quality and quantity of tumour tissue for all required tests including mutation profiling.

The Department of Medical Genomics laboratory at RPAH is currently developing an alternative way to profile cancer mutations using ultra-deep massively parallel sequencing and droplet digital PCR technologies. Instead of tumour tissue biopsy, the new method (called liquid biopsy) retrieves the cancer genomic information from blood since it contains a minute amount of DNA shed from dead tumour cells. Blood collection is simple, fast and minimally invasive. Serial analyses of circulating tumour DNA (ctDNA) become possible due to easy sampling.

The information retrieved from ctDNA can be qualitative and quantitative. The presence of an actionable mutation can be used to select treatment options in a timely manner, which is particularly useful for cancer patients with contraindications for tissue biopsy, or a biopsy with insufficient tissue for mutation profiling. Liquid biopsy overcomes the spatial heterogeneity of tissue biopsy and provides an overall view of the tumour's molecular characteristics at primary and metastatic sites. The convenience of repeat blood sampling solves the impracticability of multiple tissue biopsies. Regular monitoring of ctDNA can achieve early detection of tumour cells with a drug resistant mutation and facilitate a swift switch to an effective drug. The retrieved quantitative information makes it possible for longitudinal monitoring before, during and after clinical intervention.

The ctDNA levels of tumour-specific mutations will be measured in real time to assess treatment efficacy, prognostic indicators, guide the escalation or de-escalation of systemic chemoradiotherapy, track molecular residual disease and identify early relapses. Genomic information retrieved from ctDNA adds an important new dimension in the precision medicine-based treatment of solid tumours.

References

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Rolfo C, Mack P, Scagliotti GV, et al. Liquid biopsy for advanced NSCLC: A consensus statement from the International Association for the study of Lung Cancer. J Thorac Oncol 2021; Online ahead of print. PMID: 34246791.

Upcoming IPM&B Webinar

The IPM&B's lunch time Genomics 2021 Webinar Series wraps up later this month with Dr Abdul Baten presenting the final webinar in the series. Thanks to all who have attended so far.

Webinar 4

Bioinformatics for genome analysis

Dr Abdul Baten

Wednesday | 29 Sept | 1–2pm

IPM&B 2021 Annual Scientific Meeting: Functional Genomics

*Join us for the IPM&B's first **Annual Scientific Meeting** on Friday 19 November 2021.*

*The ASM focus this year is **Functional Genomics** with speakers including A/Prof Bruce Bennetts, Prof Marina Kennerson, A/Prof John Kwok and Dr Ira Deveson.*

The ASM will be a hybrid event (possibly 100% virtual, depending on COVID-19).

See excerpt from the ASM program below for more details.

FREE Registration now OPEN, email:
SLHD-IPM&B@health.nsw.gov.au

1:30–1:35pm Welcome: Dr Teresa Anderson AM, Chief Executive, SLHD

1:35–2:30pm **A journey from steam vents to a n=1**
Keynote speaker A/Prof Bruce Bennetts Molecular Genetics, The Children's Hospital Westmead

2:30–3:25pm **Looking beyond the exome: navigating the structural variation genomic landscape of inherited peripheral neuropathies**
Keynote speaker Prof Marina Kennerson Northcott Neuroscience Laboratory | ANZAC Research Institute
Head of Research, Deputy Director, IPM&B

3:25–3:55pm Afternoon Tea

3:55–4:25pm **Challenges & progress in the functional genomics of neurodegenerative genes**
Invited speaker A/Prof John Kwok Neurogenetics and Epigenetics Laboratory, Brain and Mind Centre

4:25–4:55pm **Comprehensive genetic diagnosis of tandem repeat expansion disorders with programmable targeted nanopore sequencing**
Invited speaker Dr Ira Deveson Genetic Technologies, Garvan Institute of Medical Research

4:55–5:00pm Concluding remarks: Prof Ron Trent, Director, IPM&B

Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

E-NEWSLETTER 27 OCTOBER 2021

Introducing IPM&B Community Representative, Dr Alan McPhail

We are delighted to welcome Dr Alan McPhail as the Community Representative for the Institute of Precision Medicine & Bioinformatics.

Dr McPhail commenced his career in the Royal Australian Navy as a technician in communications and navigational aids and then worked at the National Nuclear Magnetic Resonance (NMR) Centre at ANU. NMR is now known as Magnetic Resonance. As an engineer he continued to work with NMR and in the development of other scientific instrumentation such as rheometric and picosecond laser instrumentation at the University of Sydney. While lecturing in engineering at the University of Western Sydney he gained experience in program development and accreditation. His final appointment was as Dean, School of Engineering and Built Environment at Central Queensland University.

Following his retirement in 2012, Dr McPhail volunteered for two years at Concord Repatriation General Hospital (CRGH). He was then invited to be consumer representative for the Sydney Research Council and later the Patient and Family-Centred Care Research Working Group. By this time, Dr McPhail saw the important contribution he could make to advocate on behalf of consumers and community.

Dr McPhail now gives his time, expertise and ideas to a number of peak committees across the District. He is a valued member of SLHD's consumer network and has been involved in strategic planning, accreditation, research working groups, disability and access planning as well as consumer advisory groups for the CRGH redevelopment.

Dr McPhail has a particular interest in consumer and community involvement in research; advocating for community contributions to research and assisting to ensure research results are communicated in a way that is understandable to the community.

Consumers should be seen as partners in the research process, providing meaningful input into the planning, design, delivery and evaluation of research and clinical trials.

Dr Alan McPhail

IPM&B Annual Scientific Meeting now virtual

Due to USYD venues not opening for face-to-face events until December, the IPM&B ASM will now be held as a purely virtual event. To register, email SLHD-IPM&B@health.nsw.gov.au

1:30pm	Welcome from ***Dr Teresa Anderson AM, Chief Executive***
1:35pm	Keynote speaker ***A/Prof Bruce Bennetts***: A journey from steam vents to a n=1
2:30pm	Keynote speaker ***Prof Marina Kennerson***: Looking beyond the exome: navigating the structural variation genomic landscape of inherited peripheral neuropathies
3:40pm	Invited speaker ***A/Prof John Kwok***: Challenges and progress in the functional genomics of neuro-degenerative genes
4:10pm	Invited speaker ***Dr Ira Deveson***: Comprehensive genetic diagnosis of tandem repeat expansion disorders with programmable targeted nanopore sequencing
4:40pm	Concluding remarks from ***Prof Ron Trent, Dir, IPM&B***

From our Director

It is a great pleasure to have Dr Alan McPhail join the IPM&B where he now becomes a member of the leadership team, and will be able to provide consumer input to a range of clinical and research activities going forwards. In the short time he has been with us, I have learnt more about the value of consumer input and I hope that Alan will also get many opportunities to learn about precision medicine and bioinformatics.

I would also like to thank all who contributed to our first attempt at a webinar series on genomics, particularly, Melissa Cole, Natasha Luquin, Anthony Cheong and our Bioinformatician Abdul Baten. We even managed to include an additional webinar presented by Prof Marina Kennerson on her journey to an MRFF. Will the next journey for the Concord neurogenetics researchers be to Stockholm?

Prof Ron Trent

NSW GOVERNMENT Health Sydney Local Health District

Sydney Local Health District
Institute of Precision Medicine & Bioinformatics
E-NEWSLETTER 10 NOVEMBER 2021

Prevention with Precision

Dr Devanshi Seth *is Principal Scientist, Edith Collins Centre — Translational Research in Alcohol Drugs and Toxicology, SLHD; Associate Faculty & Head, Alcoholic Liver Disease (ALD) Research Program, Centenary Institute of Cancer Medicine and Cell Biology. As Clinical Associate Professor, she is also affiliated with the Faculty of Medicine and Health, University of Sydney (USYD).*

'My overall goal is "Prevention with Precision" to minimise disease burden at the population level and through early detection and personalised medicine at an individual level.'

Dr Seth's Alcoholic Liver Disease (ALD) Research Program established in 2010 is unique in Australia addressing several clinical and fundamental issues for a better understanding of this disease. Alcohol-related liver cirrhosis is a major cause of morbidity, mortality and hospitalisation worldwide, contributing ~50% to all liver mortality with median survival post-hospitalisation <3 years, worse than many cancers. Cessation of alcohol use prevents disease progression, but population-wide efforts to reduce alcohol consumption have made no difference to liver disease. In principle, ALD is preventable if detected early. But till now there has been no way to identify patients at higher risk of severe disease.

Dr Seth's program of work described below has significantly contributed to the knowledge and understanding of this disease leading from fundamental research to the translational domain.

Genetics of ALD. Dr Seth is the founder (2011) and leader of the multinational GenomALC Consortium studying genetics of ALD. She has twice been awarded grants by the prestigious National Institutes of Health/ National Institute on Alcohol Abuse and Alcoholism (NIH/NIAAA), USA. The GenomALC study created a large well characterised database and biobank of >6500 drinkers with cirrhosis (cases) and those without liver disease (controls). Genome Wide Association Studies (GWAS) in this cohort, and a meta-GWAS (GenomALC, UK Biobank, Buch *et al*. Nat Genet 2015 PMID 26482880) identified novel single nucleotide polymorphisms (SNPs) in *FAF2* and *SERPINA1* genes and confirmed previous SNPs in *PNPLA3*, *HSD17B13* and *TM6SF2/SUGP1* (Schwantes-An *et al*., Hepatol 2021 PMID 32853455). Interestingly, the latter are also associated with non-alcohol related liver disease, suggesting shared genetic risks between these two diseases. GenomALC investigations also revealed clinical factors associated with increasing (BMI, diabetes) and reducing (wine, coffee, cannabis use) cirrhosis risk in drinkers (Whitfield *et al*., Am J Gastroenterol 2020 PMID 32868629).

Predicting risk for cirrhosis in drinkers. Dr Seth led GenomALC study's recent paper (Whitfield *et al*., J Hepatol 2021 PMID 34656649) calculating Polygenic Risk Score (PRS) highlighting how using risk allele dosages for only three SNPs (*PNPLA3* rs738409-G, *SUGP1TM6SF2* rs10401969-C, *HSD17B13* rs6834314-G) could identify patients at high risk (3x). This novel PRS stratifies cirrhosis risk in patients, with the risk of advanced liver disease increasing >10-fold with just two risk factors (type 2 diabetes and high PRS). Communicating high (3x) and very high risk (10x) of liver disease in individual patients is more likely to engage them to respond to personal interventions. Utilisation of this polygenic risk score is a new and exciting approach for personalised risk prediction in these patients. Predicting early which drinkers are at high risk of developing cirrhosis will revolutionise clinical management of patients with alcohol use problems targeting modifiable risk factors, such as reducing alcohol use. Dr Seth's team is now advancing to implementation and translation of this world first study to test appropriateness, acceptability, effectiveness and impact of a personalised model of care for prevention of advanced liver disease.

PEth test for alcohol use. Dr Seth's program also established tests for measuring direct metabolites of alcohol (PEth, EtG and EtS) as blood biomarkers for alcohol consumption using state-of-the-art ultra-high performance liquid chromatography-tandem-mass spectrometry (UHPLC-MS/MS). PEth test is now being offered as a nationwide service in Australia for the first time. In collaboration with Chemical Pathology, RPAH and NSW Health, uptake of PEth tests are steadily increasing (~20 per month) and are routinely used by the Drug Health Services and

Liver Clinics, RPAH. PEth tests help clinicians estimate alcohol use in patients undergoing treatment for ALD, and monitor abstinence in pre-transplant and relapse to drinking in post-transplant patients. PEth is also being utilised in topiramate clinical trials for alcohol addiction at Drug Health, RPAH.

Gene functional studies. It is intriguing that several SNPs, in *PNPLA3*, *HSD17B13*, *TM6SF2* and novel *FAF2* associated with risk of cirrhosis, are involved in the lipid droplet biology and lipid metabolism pathways. However, functions of these SNPs/genes in the progression of disease remain unclear. Dr Seth's world leading research in this field has established an *in vivo* zebrafish model of acute alcohol-induced fatty liver at the Centenary Institute. Using CRISPR-Cas9 genome editing, Seth laboratory has created zebrafish embryo knockdowns for orthologs of *faf2*, *pnpla3*, and *serpina1*. Early data shows knocking down these genes increased susceptibility to acute alcohol toxicity, lipid accumulation in the liver, hepatic neutrophil infiltration and reduced survival following high dose alcohol exposure (Oehlers *et al*., AASLD 2020). This ongoing research will help understand the role of lipid droplet genes in disease development with potential to identify novel drug targets.

Champion for Inclusion, Diversity, Equity. Dr Seth is a passionate advocate of Inclusion, Diversity, Equity (IDE) and has made significant contributions through mentoring and leadership in this area. Dr Seth is the founding Chair of the Inclusion Gender Equity Program (IGEP) at the Centenary Institute and has made headway on several initiatives benefitting staff. She received the Team Excellence Award for leading IGEP (2015-2018). As a lifetime member of Franklin Women (FW) and on FW Peer Advisory committee, Dr Seth helped develop FW Mentoring Program, the most successful and sought-after mentoring program in this sector, now running in its 5th year. She herself was FW Mentor in 2018. She reviews applications for biannual FW Carer Scholarships and helps with FW events focusing on leadership training for EMCRs. As USYD SAGE-SAT member, she is assisting with planning the Cygnet award application and monitoring the implementation of IDE Action Plan of the Athena SWAN Award. Internationally, she is the Lead of the Research Society on Alcoholism (USA) Diversity sub-committee focusing on the inclusion of diverse research subjects, projects and researchers in alcohol research.

For Honors and PhD opportunities in this research area, contact Dr Seth via email – d.seth@sydney.edu.au

From our Director

As this is the final e-Newsletter of the year, I wish all members of the IPM&B a happy and safe Christmas as well as a new beginning for 2022 in which COVID-19 takes a minor place to a back to normal life at home and work. As 2021 progressed, it was impressive to see our health colleagues take on extraordinary duties to deal with COVID-19 and still continue their daily work. They were all very inspirational.

Work with the IPM&B progressed and for that I am grateful to a team of supporters; particularly Melissa Cole (Operations Manager), Natasha Luquin (Honorary Chief Scientist), Clement Loy (Deputy Director), Marina Kennerson (Deputy Director) and Alan McPhail (Consumer Representative). Also thanks to our Genomics Bioinformatician Abdul Baten who was ably supported by Anthony Cheong (Genetic Pathology), Harry Iland (Molecular Haematology), Hugh French (Genetic Pathology Registrar) and Sebastiaan van Hal (Molecular Virology). David Sullivan (Chemical Pathology) continued to provide new ideas on the way forward!

Prof Ron Trent

Don't miss the IPM&B Annual Scientific Meeting next week

The IPM&B's first ASM will be held virtually next Friday 19 November. Welcome from SLHD CE ***Dr Teresa Anderson AM*** *at 1:30pm, and speakers including* ***A/Prof Bruce Bennetts***, ***Prof Marina Kennerson***, ***A/Prof John Kwok*** *and* ***Dr Ira Deveson****. Registration and program details for this free event by email to SLHD-IPM&B@health.nsw.gov.au*

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