Annual Report 2023

Innovative health care and research utilising precision medicine

Published: March 2024

NSW GOVERNMENT

The Institute of Precision Medicine & Bioinformatics (IPM&B), established in March 2020, is a strategic institute facilitating clinical and research work in precision medicine within Sydney Local Health District (the District). The IPM&B provides a clinically relevant home for health professionals working in genomics in the District. Bringing together clinical, laboratory, research and bioinformatics expertise in genomics, the Institute's vision is to ensure the benefits of precision medicine are rapidly and effectively implemented into the clinical care of patients and their families.

Our Annual Report 2023 is a review of our achievements and highlights over the last year and includes information about our activities and performance.

Acknowledgements

2023 was a successful year for the IPM&B with many contributing generously to progress key initiatives. The IPM&B bioinformatics team met regularly and included Drs Abdul Baten, Anthony Cheong, Hugh French, Professors Harry Iland, Seb Van Hal and Bing Yu. We were fortunate to interact with the District's Digital Health Innovation team and, in particular, I acknowledge ongoing support of Mitch Burger and David Norwood. The support of the IPM&B Executive Leadership Team is appreciated. I would particularly like to thank our Consumer Representative, Dr Alan McPhail, who led the formation of the Precision Medicine Consumer Group in 2023. I thank the members of the IPM&B Strategic Advisory Council for their high level advice and Melissa Cole, Operations Manager, for her contributions across many administrative and policy activities.

As Director, I am in the fortunate position to interact with many organisations. Our staunchest supporter remains Sydney Local Health District and its associated RPA and Concord Hospitals. Working with talented clinicians in precision medicine continues to provide a stimulating environment. Little of the above would be possible without the guidance and encouragement of our Chief Executive Dr Teresa Anderson AM, who is ably assisted by Chief of Staff Hannah Storey and the District's Executive Support Unit.

Professor Ron Trent
Director, Institute of Precision Medicine & Bioinformatics

Front cover:
Stipe Zekanovic, Hospital Scientist
Department of Medical Genomics Laboratory
RPA Hospital

Institute of Precision Medicine & Bioinformatics Head Office

Address:
Royal Prince Alfred Hospital
Building 65, Level 6
Missenden Road
Camperdown NSW 2050

Phone: 02 9515 5300
Fax: 02 9515 5500

Email:
SLHD-IPM&B@health.nsw.gov.au

Web:
slhd.health.nsw.gov.au/ipmb

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Contents

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 the 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 Land 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.

Year in Review

Message from the Director

Professor Ron Trent

Clinical Institutes Forum

Sydney Local Health District's clinical institutes are centres of excellence, created by bringing together health professionals under a unifying theme to facilitate the integration of research and education directly into clinical care. Some of the District's institutes are focused to RPA and Concord Hospitals while the activities of others extend across all facilities.

2023 saw the addition of a new forum to Innovation Week showcasing the work of these institutes. The *Clinical Institutes – Bridges to Innovation* event highlighted the breadth of talent available within the District to address clinical challenges and develop strategies and models of care providing solutions. Featured institutes were:

- **ANZAC Research Institute Concord**
  A biomedical research institute operated in honour of veterans and their families. Supports innovative collaborative research linking scientists, clinicians and community.
- **RPA Green Light Institute**
  A hub for collaborative and translational research in emergency medicine. Focuses on high impact acute medical conditions including trauma, stroke, cardiac, mental health and sepsis.
- **Institute for Musculoskeletal Health (RPA Hospital & University of Sydney)**
  A focus on optimising musculoskeletal health and promoting physical activity in health, aged care and community settings. Currently hosting 27 higher degree research candidates, 182 peer reviewed publications in 2022.
- **RPA Institute of Academic Surgery**
  Supports and promotes surgical research and education through innovative programs, initiatives and technology.
- **Concord Institute of Academic Surgery**
  Utilises the diversity of interprofessional surgical teams to lead innovative solutions to key surgical challenges. Supports surgeons and researchers to foster international collaborations and transform evidence into implementation practices.
- **Sydney Institute for Women, Children and their Families**
  A central hub for research, education and policy relating to health and social well-being of women, children and their families. Multidisciplinary research environment is promoted across Sydney Local Health District, affiliates and partners.
- **RPA Institute for Academic Medicine**
  The linkage between research, teaching and clinical care leads to an exemplary cycle of discovery, innovation and excellence in healthcare. Supporting clinicians and researchers to ensure RPA Hospital continues its leadership role in patient care.
- **SLHD Institute of Precision Medicine & Bioinformatics**
  Facilitating the practice of precision medicine to drive innovative models of research, clinical care/prevention, and building capacity in bioinformatics.
- **SLHD Edith Collins Centre**
  Australians are widely exposed to alcohol drugs and toxins leading to a major impact on health and healthcare services. The Edith Collins Centre focuses on translation of evidence into better treatment in hospitals and the community.

The clinical institutes have continued to meet following the forum, to collaborate more effectively in their important work.

Biological and designer therapies

The 2023 Nobel Prize for Medicine or Physiology went to researchers Katalin Kariko and Drew Weissman, from the USA, for their work on mRNA vaccines that were ultimately used in COVID-19.

This highlighted the importance of the growing number of biological and designer therapies, such as mRNA, monoclonals, cancer inhibitors, gene and cellular therapies (including CAR-T cell therapy).

These therapies are fundamental to the roll out of precision medicine, which is not simply an investigative model of care, but the application of knowledge from genomics and other omics to enable novel interventions selected on the needs of individual patients.

Sydney Local Health District is well placed to administer these new therapies through its impressive Department of Cell and Molecular Therapies at RPA Hospital, headed by Professor John Rasko AO (pictured). The timely introduction of the District's Preparation of Pharmaceutical & Advanced Therapeutic Products Steering Committee will implement recent policy directives from NSW Health to enable the delivery of novel therapies in NSW public health facilities.

Molecular Medicine at Concord Hospital

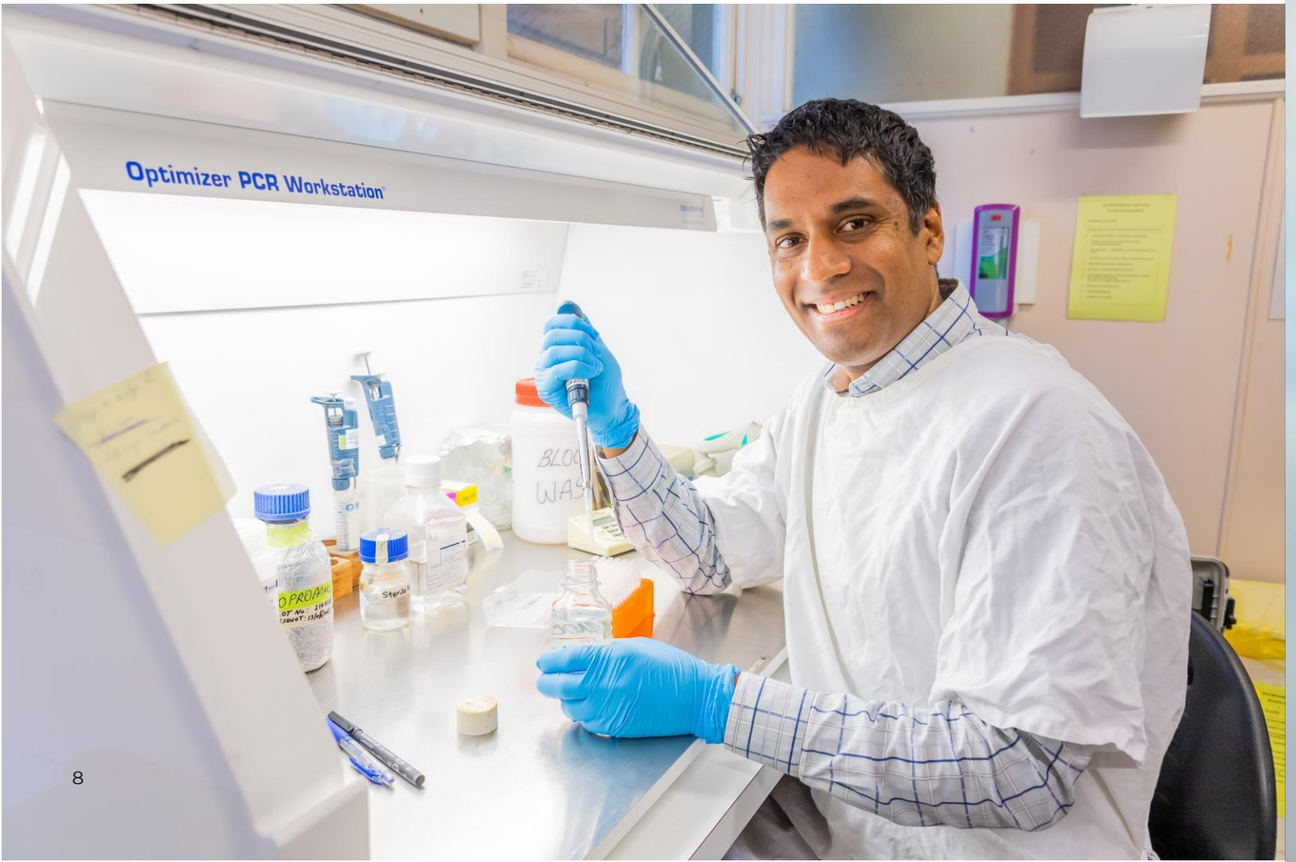
The role being played by the IPM&B at Concord Hospital's Molecular Medicine Laboratory is worthy of review in 2023.

A few years ago, there was a meeting of representatives from NSW Health Pathology, Concord Hospital and Sydney Local Health District to discuss the future of this important neurogenetics laboratory, founded by Professor Garth Nicholson.

With Garth's retirement, the issues of concern were ongoing supervision and the viability of a relatively small laboratory administered by NSW HP which, from an organisational perspective, was more focused to comprehensive State-wide based services. At this meeting, there was no clear way forward until the District's Executive Director of Operations proposed a new staff specialist genetic pathologist position be created and funded by the District to enable the RPA Molecular Genetics Laboratory and the Concord Molecular Medicine Laboratory to work together more closely while remaining independent in their interests.

Dr Anthony Cheong was appointed as genetic pathologist and now spends 1.5 days per week at Concord and the remaining time at RPA Hospital. Joint supervisory arrangements are working well and during 2023 it was pleasing to see both laboratories have benefited from this arrangement.

At the end of the aforementioned meeting, the representative from NSW Health Pathology commented that he did not think any other Local Health District, apart from Sydney, would have come up with such a generous offer to ensure genomic pathology at Concord would continue and prosper. See Our Stories for a perspective of neurogenetics work at the Concord Molecular Medicine Laboratory from Associate Professor Kishore Kumar (pictured).



Transcriptomics

A noteworthy milestone during 2023 was the integration of transcriptomics into precision oncology at Sydney Local Health District. This was led by Associate Professor Bing Yu and the Somatic Cell DNA Testing Service, which now utilises RNA to detect fusion genes in solid tumours

Although an uncommon mechanism causing cancer, fusion genes are clinically important and must be detected before patients can access a range of anti-cancer treatments through the PBS (see Somatic Cancer Testing for more information on fusion genes).

Two other noteworthy initiatives during 2023 included the formation of the Precision Medicine Consumer Group led by IPM&B Consumer Representative, Dr Alan McPhail. This small, but enthusiastic group, has already provided important insights from the consumer's perspective on IPM&B initiatives, including the development of a pharmacogenomics model of care for Sydney Local Health District. See Consumer engagement in precision medicine, where Dr Alan McPhail describes the group's activities in more detail.

Another important and growing relationship is that established in 2023 between the IPM&B and Sydney Local Health District's Digital Health & Innovation team. See Future Directions where these collaborative projects are described in more in detail.

Director
Professor Ron Trent

2023 Activity

Somatic Cancer Testing Service

Highlights

- After achieving accreditation in late 2022, the Somatic Cancer Testing Service began 2023 with the implementation of a brand new test offering to all patients referred to the service. The new test is performed using next generation sequencing (NGS) and screens for clinically actionable variants in 20 cancer related genes. While previous testing only looked for known variants in fewer genes, this test looks for unknown variants across large regions of genes, unlocking clinically significant information for diagnosis and prognosis as well as support for clinicians in their treatment decisions.

- Importantly, we can offer DNA-based assessment of variants in the MET gene that cause exon skipping and is targetable by the PBS-available drug tepotinib in patients who have non-small cell lung cancer. We also see detailed sequence changes in the EGFR and ERRB2 genes, which can better stratify treatment options for lung cancer patients. For our melanoma patients, we can provide prognostic information for patients who have alterations in the TERT gene.

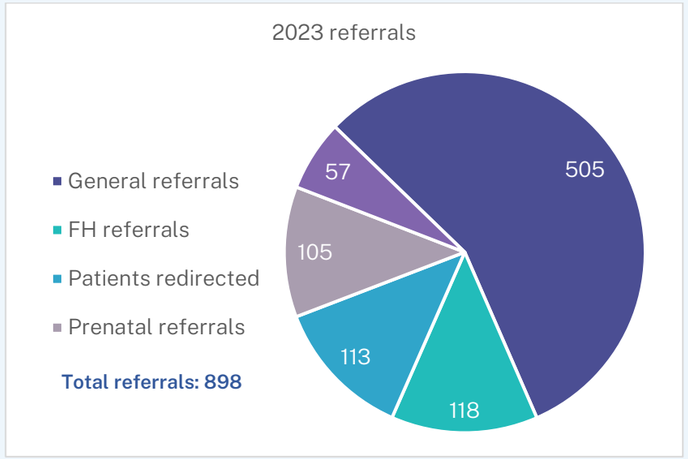
The diversity of variants we have curated beyond the Medicare-rebated targets has provided more opportunities for patient eligibility in clinical trials.

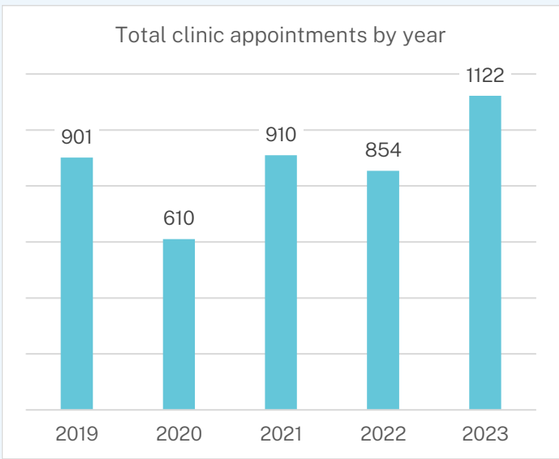
- Somatic mutation testing for solid tumours expanded from DNA-based to DNA- and/or RNA-based NGS analysis. Our RNA-seq fusion NGS test for solid tumours was formally endorsed on 29 May 2023 by NSW Health Pathology. With the hard work of the team, we successfully extracted RNA from formalin-fixed paraffin embedded (FFPE) tissue that is suitable for down-stream analysis. The relevant quality metrics were also established to ensure the accuracy and reliability of the RNA-based test. FFPE RNA extraction and RNA-based MET exon skipping assays were successfully accredited by NATA in August 2023. The artificial intelligence-based prediction of splice-affecting variants was validated and accredited by NATA. Further validation of hybridisation capture-based and amplicon-based RNA-seq assays was undertaken throughout 2023, which will expand the service offering further in 2024, and detect fusion genes, splicing consequence, and high gene expression.

Clinical Genetics Service

Highlights

During 2023, the Clinical Genetics Service triaged 898 new referrals, 65% of the referrals were accepted and 35% of the referrals received were either assisted via phone, redirected to other services or were not seen at this service.





During 2023, the Clinical Genetics Service carried out 1,122 consultations (both face to face and telehealth) with prenatal, neonatal, paediatric, and adult patients.

IPM&B Engagement and education

Highlights

103 attendees to IPM&B events	48% increase LinkedIn followers	New IPM&B website launched
353 attendees to IPM&B webinars	968 opens IPM&B e-News	21% increase X followers

Our Services

Somatic Cancer Testing

Precision Oncology: Targeting fusion genes in adults with solid tumours

Fusion genes account for around 17% of morbidity in solid tumours, despite being less common[1]. In recent years, we have seen an increase in clinical trials and publicly funded drugs that target gene fusions in solid tumours. Additionally, fusion genes can be helpful biomarkers for resistance to targeted treatments[2]. Unlike more common gene alterations, fusion genes could be very specific to tumour types and can help pathologists to determine a diagnosis[2]. With improved technologies and bioinformatics, fusion gene testing in routine clinical care of cancer patients has increased in importance, and this is reflected by the recommendations for fusion gene testing in clinical guidelines for lung, colorectal, thyroid cancer, prostate, breast and gynaecological cancers (nccn.org).

Treating fusion-gene solid tumours in Australia

Currently there are seven drugs funded by the Pharmaceutical Benefits Scheme (PBS) that target fusion genes in solid tumours (Table 1). Most well-known is Crizotinib, which is effective in targeting lung cancers that harbour *ALK* as well as ROS1 rearrangments[3, 4]. Ceritinib, alectinib and lorlatinib also target both *ALK* and *ROS1* fusion genes, however only *ALK*- positive non-small cell lung cancer (NSCLC) is funded. Entrectinib is approved for *ROS1* positive NSCLC only in Australia, however is FDA approved overseas for many solid tumours as it is also effective in *ALK*, *NTRK1*, *NTRK2* and *NTRK3* fusion positive solid tumours (nccn.org). There are several clinical trials available in Australia covering a broad range of solid tumours with various fusion genes (Table 1).

Challenges in detecting Oncofusions in a clinical setting

Traditional methods for fusion detection in clinical settings are becoming less practical to apply. Immunohistochemical (IHC) assessment is a fast screening tool, but less specific. Fluorescence in-situ hybridisation (FISH) is highly specific but limited to known breakpoints. Both methods require additional tissue for each target[5].

Next generation sequencing (NGS) methods can employ multi-fusion detection[6] and take advantage of both DNA and RNA extraction from a single sample. In practice, we use patient biopsies that are treated with formalin (called FFPE tissue) and this contributes to degraded RNA quality or quantity and a test failure rate of ~ 15-26%[6-8]. In Figure 1 below, the best RNA comes from fresh tissue (in green), where most fragments are more than 200 nucleotides long. The greater the proportion of fragments shorter than this, the poorer the quality.

Fusion gene testing in solid tumours of up to 16 fusion-genes will be available in 2024.

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4. Shaw, A.T., et al., *Crizotinib in ROS1-rearranged non-small-cell lung cancer.* N Engl J Med, 2014. 371(21):1963-71.
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Drug	Fusion Gene Target	Solid tumour type	Access in Australia
crizotinib	ALK, ROS1	NSCLC	PBS
ceritinib	ALK, ROS1	NSCLC	PBS (ALK only)
alectinib	ALK, ROS1	NSCLC	PBS (ALK only), NCT05170204
lorlatinib	ALK, ROS1	NSCLC	PBS (ALK only)
brigatinib	ALK	NSCLC	PBS
entrectinib	ALK, ROS1, NRTK1/2/3	NSCLC (FDA approved for solid tumours)	PBS (ROS1 NSCLC only), NCT05170204
Cabozantinib	RET	Renal cell, NSCLC, thyroid	PBS (RCC only)
larotrectinib	NTRK1, NTRK2, NTRK3	Solid tumour	PBS
Durvalumab	ALK Wild-type only	NSCLC	NCT05170204
Selpercatinib	RET	NSCLC, thyroid, colon and solid tumours	NCT04819100, NCT03899792, NCT03157128
Pralsetinib	RET	NSCLC	NCT04222972

Table 1. Drugs targeting solid tumours with fusion genes in Australia. Only clinical trials where drugs appearing on the Australian Register of Therapeutic Goods (ARTG) have been included. Sourced from pbs.gov.au, australianclinicaltrials.gov.au, tga.gov.au.

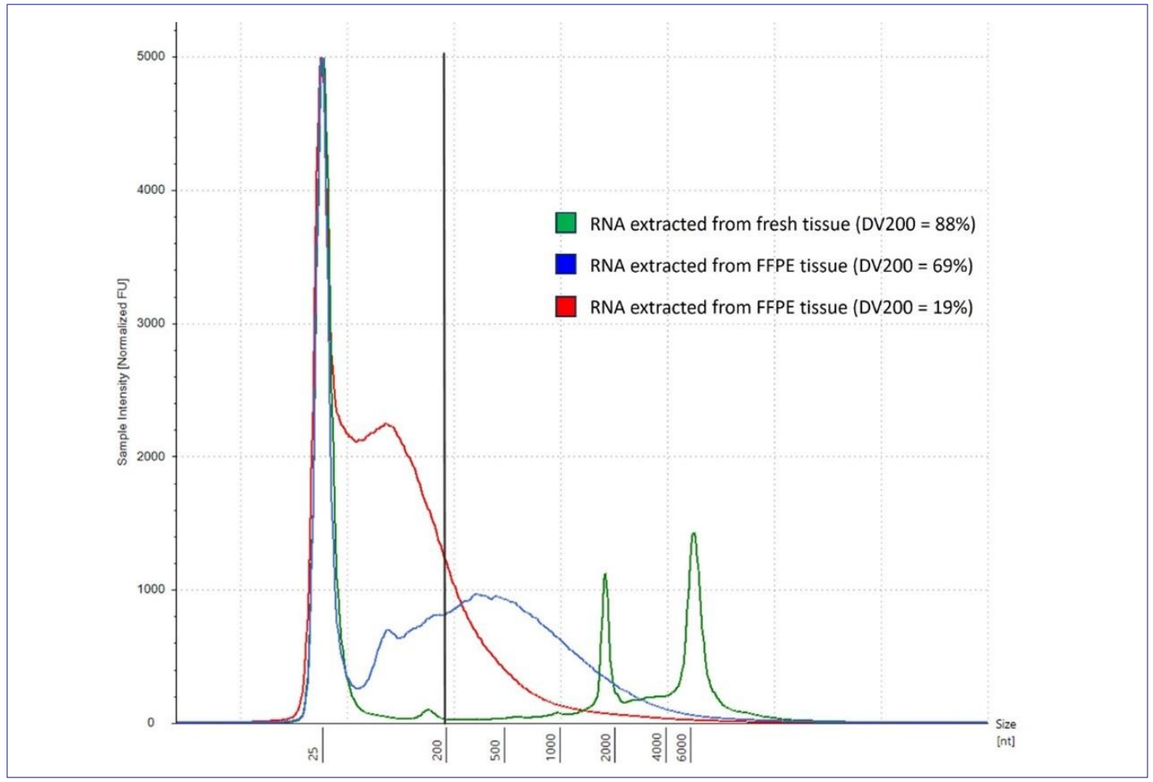

Figure 1. Comparison of RNA quality from fresh tissue (green), and FFPE tissue (red and blue). The red graph indicates FFPE-RNA that is poor quality and the blue graph indicates FFPE-RNA which is acceptable quality.

Clinical Genetics

The Clinical Genetics Service at Sydney Local Health District carries out outpatient and inpatient consultations with adult, paediatric, neonatal and prenatal patients. The range of patients seen includes those with a suspected or confirmed genetic condition, as well as family members who may be at risk of an inherited condition. The service provides genetic assessment, genetic counselling and facilitates genetic and genomic testing as appropriate. The Clinical Genetic Service works closely with many other specialties, often in the form of multidisciplinary clinics, to provide integrated and timely genetic assessment and counselling for patients with a wide range of genetic conditions. These multidisciplinary clinics include renal genetics, neurogenetics at RPA and Concord Hospitals, aortopathy and Marfan Syndrome, adult congenital heart disease, genetic eye disease, interstitial lung disease and endocrinology clinics. In 2023, clinical genetics services were integrated into the newly established Hereditary Haemorrhagic Telangectasia MDT Clinic.

The Clinical Genetics Service includes four Clinical Geneticists (2.5FTE): Dr Lisa Worgan (Head of Service), Dr Felicity Collins, Dr Amali Mallawaarachchi and Dr Alison McLean. Dr McLean commenced as a staff specialist in clinical genetics in 2023 and is already a highly valued member of the team. The genetic counselling team includes Kathleen Le Marquand, Laura Molloy and Shona Reid (3.0FTE). Claire Trumble and Madeleine Calder filled the 1.0FTE Genetic Counsellor position in 2023 that provided services to the Hyperlipidaemia and Porphyria clinics. The Clinical Genetics Service is supported by administrative staff (2.8FTE); Panayiota Tsaglakis, Rayaca Tayabally and a currently unfilled administrative position to be recruited in 2024.

A new Clinical Genetics Advanced Trainee position was supported by Sydney Local Health District for appointment in 2024 for one year. This is a very exciting opportunity for training in clinical genetics with exposure to prenatal, paediatric and adult subspecialty genetic medicine, and will advance both academic and clinical service provision within the District. Dr Rachel Bowden will start in February 2024 in this position.

In 2023, the Clinical Genetics Service maintained its commitment to providing equitable and excellent clinical care for patients. The establishment of genetic counsellor led clinics and developing new ways of working with MDT clinics has enabled easier and more timely access to clinical genetics services for many patients.

In 2023, access to genomic testing became more accessible for other health providers with the establishment of Medicare Rebates for genetic testing for some specified conditions. Clinical genetics continues to provide support to non-genetic specialists in obtaining consent, ordering appropriate tests and interpreting genetic test results. This is moving towards the future when many genetic tests will be “mainstreamed”, and the future workforce will need upskilling in the appropriate application of these technologies.

Commitment to education

The Clinical Genetics Service contributes to teaching at all levels, including for junior medical staff, Sydney University medical students and UTS Master of Genetic Counselling students.

- Drs Collins and Worgan are Learning Advisors for University of Sydney medical students
- Drs Collins and McLean are teachers in the RPA Hospital BPT exam preparation course
- Dr Collins delivers two cystic fibrosis lectures in the University of Sydney Masters of Genomic Medicine Course. Dr McLean provides a pharmacogenomics lecture to the same course
- Kathleen Le Marquand, Laura Molloy and Shona Reid supervise genetic counselling students on clinical placements. Kathleen also has a position at the University of Technology as a lecturer for the Master of Genetic Counselling course
- Dr Amali Mallawaarachchi supervised an MD student project in 2023.

Committee roles

- Dr Lisa Worgan continued as Co-Chair of the NSW Health Agency for Clinical Innovation Clinical Genetics Network Executive Committee. This group is commited to identifying key priorities to achieve effective and equitable genetic services across NSW. In 2023, work was focused on models of care in MDT clinics, reviewing and updating NSW health policies pertinent to clinical genetics and working groups involved in implementation of the NSW Genomic Strategy.
- Dr Felicity Collins continues to participate in the Clinical Genetics Services committee of the Human Genetics Society of Australasia, undertaking a review of the policy document for Clinical Genetics Services Framework, due for release in 2024.
- Dr Amali Mallawaarachchi is co-chair of the National KidGen Kidney Genetics MDT, that provides expert diagnostic and management advice for genetic kidney disease families.
- Dr Mallawaarachchi is a Research Lead for the Institute of Academic Medicine at RPA Hospital and expert panel member on the international NIH-funded ClinGen Gene Curation Expert Panel in Cystic Kidney Disease.
- Dr Mallawaarachchi is also part of the Leadership Team for the Clinical Academic Group in Genomics and Precision Medicine Partnerships, funded through Sydney Health Partners.
- Dr Alison McLean continues to participate in the Education, Ethics and Social Issues Committee as part of Human Genetics Society of Australasia, responsible for drafting and updating policy documents under HGSA.
- Dr McLean contributed to the Australasian Association of Clinical Geneticists Executive Committee.
- Dr Mallawaarachchi is Deputy Chair of the Education and Training Committee for the Australian and New Zealand Society of Nephrology.

Genetic counselling

Kathleen Le Marquand is the senior genetic counsellor for Sydney Local Health District and represents genetic counsellors as the lead for their allied health group reporting to the District’s Allied Health Director. She also sits on the NSW Genetic Counsellor Advisory Group, whose aim is to ensure the equity of genetic counselling services across NSW Local Health Districts and the promotion of genetic counselling services.

Kathleen is the clinical supervisor for the team of genetic counsellors at the IPM&B, consisting of Laura Molloy, Shona Reid, Claire Trumble and Madeline Calder. Laura is currently the Chair of the HSU Genetic Counsellor Committee, tasked with working on a new award structure for allied health professionals.

Kathleen continues to represent genetic counsellors on multiple committees. She is currently the Chair of the HGSA Professional Issue Committee for genetic counsellors and Chair of the Professional Complaints and Concerns Committee. In order to balance Kathleen’s clinical work, she is the Deputy Chair of the board of directors for Genetic Alliance Australia, a non-profit organisation for individuals and families affected by rare disease.

Kathleen, Laura and Shona attended a special meeting in Canberra at Parliament House in November 2023 representing their profession for Genetic Counsellor Awareness Day. As a team they promote genetic counselling services throughout the District working with many clinical specialities.

Bioinformatics

Dr Abdul Baten
Genomics Bioinformatician, IPM&B

Whole exome sequencing

RPA and Concord Hospitals received NATA accreditation in 2022 to provide gene panel testing on a whole exome sequencing backbone. A bioinformatics workflow was designed for the quality control (QC) of raw sequencing reads, binary alignment and mapping (BAM) files, and variant call format files.

Importantly, we have an additional process in place to ensure the integrity of DNA samples and sequencing data is not compromised. The Agena Custom Exome QC Panel – iPLEX® Pro UK Exome QC Panel is a custom-designed panel used for sample identification and DNA quality control. Sample identification is achieved by genotyping 23 exonic identity single nucleotide polymorphisms and 3 gender markers. This assay is used to verify the identities of extracted DNA samples from both RPA and Concord Hospitals, as well as sequencing data from either NSW Health Pathology statewide sequencing service or elsewhere.

Once the genotype calls are available, they must be checked against the exome sequencing data. A bioinformatics workflow, which is a combination of several command-line utilities along with a graphical user interface, has been developed to:

- call the genotype from the exome sequencing data (extracted from the alignment BAM file),
- compare the genotype calls against the genotype calls in the QC panel (Agena), and
- generate a report summarising the results. The sample integrity check method is also verified to determine if a sample is altered, wrongly labelled, if genotype calls are incorrect, and whether we can identify them.

Cloud-based analysis server

Cancer is a genetic disease characterised by mutations in the genome that lead to uncontrolled cell division. Precision medicine necessitates the targeting of these specific mutations with specialised drugs, a process achievable only through the identification of such mutations in tumor samples via genetic testing. This testing involves scanning the DNA or RNA extracted from tumor or blood samples using next generation sequencing, generating vast amounts of data that must be rapidly processed to facilitate the prompt prescription of the appropriate drug. Our laboratory conducts analyses on a weekly basis, handling anywhere from 10 to 48 samples simultaneously. This requires a few hours of computational time to process all samples in parallel efficiently and cost-effectively. The analysis pipeline demands moderate computing resources (1 CPU and 12 GB RAM per sample). When installed on a local server, its usage is constrained by the available RAM and CPU of that server. For instance, running a batch of 30 samples would necessitate 30 CPUs and 360 GB RAM. The fluctuating number of samples in each run renders it suboptimal for a local server.
A large, static virtual machine utilised only a few hours a week proves cost ineffective. With assistance from the Sydney Local Health District's Department of Digital Health and Innovation team, we have implemented a cloud-based analysis pipeline. This solution provides scientists with the flexibility to launch a virtual machine based on the number of samples in each run, ensuring optimal resource utilisation. Through the utilisation of Microsoft Azure and function apps, diagnostic scientists can independently resize the virtual machine running the analysis software, minimising the need for IT support intervention. This enables the simultaneous processing of all samples, ensuring timely reporting of genetic variants and allowing patients with cancer to receive the appropriate treatment sooner.

AI educational initiative

The symbiotic relationship between healthcare and AI technologies is reshaping the landscape of medical practices, making it imperative for health professionals to possess a fundamental understanding of these cutting-edge tools. The integration of AI in healthcare necessitates interdisciplinary collaboration between technologists and healthcare professionals. A shared understanding of AI concepts facilitates effective communication between these two domains, fostering collaborative efforts to address complex healthcare challenges. Doctors, scientists, and other health professionals with AI knowledge can actively participate in the development and refinement of AI applications, ensuring these technologies align with clinical needs and ethical standards. Following the IPM&B's Cloud Computing Forum, where attendees sought information about clinical applications of AI, we initiated discussions with Sydney University's Biomedical Informatics and Digital Health group to engage educational activities such as seminars, lecture series and micro-credentials on AI and related topics.

Education in AI could play a pivotal role in unlocking the full potential of these technologies in healthcare, enabling professionals to provide better, personalised care, streamline operations, and navigate the ethical challenges of this rapidly evolving landscape. Embracing AI education today is an investment in a healthier and more technologically empowered future for healthcare.

Molecular Medicine

Dr Anthony Cheong
Genetic Pathologist, IPM&B

Highlights

The team at Concord Molecular Medicine Laboratory saw a significant uptake in genomic testing for neuromuscular diseases in 2023, as the new MBS items for gene panels and single gene testing are now in effect. Compared to 2021, the laboratory received an almost 50% increase in referrals. The number of gene panel requests has increased eight-fold to >600 requests in 2023.

The rapid increase in referral numbers has placed significant pressure on the turnaround time and laboratory staffing. Despite the pressure, the team has performed well in the external quality assurance program, scoring full marks in the assessment. To address the issue of turnaround time, reporting is prioritised to ensure positive reports are delivered in a short period. Feedback from referrers has been positive and the team was nominated for a NSW Health Pathology award in 2023.

However, it is the negative report that actually takes longer as the assessment and safe dismissal of rare but irrelevant or non-pathogenic variants, often with little information on their potential effect, remains a relatively manual process. This process cannot be achieved by interrogating the genetic data alone, and the correlation between clinical information and genetic data currently relies heavily on human input. This would be an example where incorporation of multimodal artificial intelligence could potentially improve efficiency.

The laboratory celebrates the successful MRFF grant application led by Associate Professor Kishore Kumar. The Monogenic Parkinson's Disease Australia (monoPDAus) Initiative research project aims to improve the genetic diagnosis of monogenic Parkinson's Disease through the accurate identification of disease-causing variants in known genes and the discovery of novel genes. The laboratory will be involved in the data analysis and clinical validation on discoveries. Our ongoing collaboration with the clinical team at Concord Hospital and ANZAC Research Institute will provide clinical assessment, diagnostic service and research study under one roof.

Pharmacogenomics

Professor Ron Trent
Director, IPM&B

Dr Branka Powter
Chief Scientist, IPM&B

Pharmacogenomics (PGx) has been investigated for many years but remains to be fully implemented or even introduced into some models of clinical care (MoC). In Australia, possible barriers to implementation include:

- Equivocal reports on the efficacy of PGx, for example, a recent study implies that PGx for cancer drugs is well proven, but more evidence is needed for non-cancer therapeutic uses (Kim et al, *J Pers Med* 2021;11:179). In contrast, another study to assess a comprehensive 12 gene PGx panel showed a significant reduction in adverse drug reactions across multiple drug types (Swen et al *Lancet* 2023;401:347).
- Since 2000, the USA's FDA has taken a more proactive approach to labelling drugs with PGx information whereas the TGA in Australia has been less active. This may change as the Royal College of Pathologists of Australasia has now taken up the challenge by looking into the development of recommendations for *Clinical indications for PGx testing in Australia*.
- US health insurance providers are interested in cost savings through PGx and so promote and fund this activity. Medicare in Australia works through genetic tests being funded by the MBS which means the process involved can be slow leading to a few HLA based PGx tests and TMPT PGx testing as the examples easily accessible in Australia.
- For the purpose of clinical utility, a genetic test result must be linked to a therapeutic decision which can be complex. Nevertheless, there are a growing number of international resources such as Clinical Pharmacogenetics Implementation Consortium bridging the gap between a test result and clinical actions required.

A long-term interest of the Department of Medical Genomics at RPA Hospital has been PGx and finally in 2023 the Department obtained NATA ISO 15189 certification to provide a comprehensive PGx testing service. The laboratory journey to this point was long and challenging and would not have happened without support and funding from Sydney Local Health District to the IPM&B. In particular, we would like to acknowledge the contributions of Drs Natasha Luquin and Lan Nguyen.

The next leg on this journey will be focused to the type of service provided and how to report PGx findings. This discussion started with the IPM&B's Annual Scientific Meeting in late 2023 when a group of experts met to consider what might comprise a suitable MoC for PGx at Sydney Local Health District. Disciplines represented included psychiatry, cardiovascular, clinical chemistry, pharmacy, health economics and clinical genetics. The MoC is now being finalised and is likely to provide gene panel-based testing selected on the basis of organs / diseases / research interests.

It is envisaged that there will be separate PGx testing panels for:

- cardiometabolic therapies
- cancer therapies
- pain therapies and
- mental health therapies.

Therefore, the reporting templates will be simplified to enable easier implementations across different medical professions, and directly contribute to increased efficiency in patients' treatment. Watch this space as the PGx MoC at Sydney Local Health District evolves over 2024-2025.

Consumer Engagement in Precision Medicine

Dr Alan McPhail
IPM&B Consumer Representative

On 11 May 2023, a group of Sydney Local Health District consumer representatives and volunteers were welcomed to the IPM&B's Consumer Engagement in Precision Medicine Workshop. The goal of the workshop was to provide an opportunity for health consumers and community members to meet, mingle and learn about precision medicine and its application at Sydney Local Health District.

IPM&B Consumer Representative Dr Alan McPhail shared his experience of involvement in health research and outlined the support and mentoring available for consumers interested in being involved. The group also heard insights from IPM&B Director, Professor Ron Trent and Sydney Health Partners Research Director, Associate Professor Angela Todd.

Following the workshop, we established the Precision Medicine Consumer Group. The group has continued to meet every three months, with the aim to provide further information about precision medicine, research projects and opportunities for health consumer training.

Highlights from the group's subsequent meetings in 2023 included:

- Prof Ron Trent outlining the IPM&B's commitment to consumer involvement in research
- Dr Alan McPhail discussing the role of the consumer and community in research and how their experiences can contribute to the processes of research.
- Operations Manager, Melissa Cole providing the group with details of introductory health consumer training programs
- Genetic Pathologist Dr Anthony Cheong presenting a patient story which illustrated the impact of precision medicine on patient care.

It was very interesting to hear how the diagnosis of a genetic condition and targeted treatment resulted in a major improvement in the quality of life for the patient.

- An update on the work of the Consumer Advisory Panel (CAP) of Sydney Health Partners (SHP). The CAP is working on a plan for the components that need to be addressed to ensure that consumers and community are prepared for involvement in research. The components are Governance, Capacity Building, Leadership, Infrastructure and Monitoring. Capacity building includes training, and events; Leadership includes preparing Consumer Champions for the role; and Infrastructure is investigating the necessary attributes and design of a database. The outcomes of this work will be available to all the partners of SHP, including Sydney Local Health District.
- An outline of the Principles for Consumer Involvement in Research Funded by the Medical Research Future Fund.
- Upcoming research projects planned at the IPM&B, including a project focused on youth with mental health illness and the role of pharmacogenomics. The variation in particular genes may affect the outcomes of the use of pharmaceuticals.

We now have a keen group of consumers who want to be involved in research and 2023 has been an excellent start to our project.

IPM&B members are welcome to contact the Precision Medicine Consumer Group if they would like consumer input into a research project or feedback on a new model of care.

Artist Impression: Sydney Biomedical Accelerator (SBA)

Research & Innovation

Omics Research

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

Challenges and solutions for leveraging advances in omics research

Research activities at the IPM&B are continuing to embrace the ongoing advancement of “omics” technologies (genomics, epigenomics, transcriptomics, proteomics, metabolomics, and pharmacogenomics) as the cornerstone for advancing personalised medicine and facilitating patient care. For genomic precision medicine, the impact of improved and affordable long read sequencing technologies along with the changing landscape of genomic reference genomes has spearheaded an exciting research frontier for gene discovery and addressing gene variants of unknown significance. However, with these advances come the challenges of cost and handling the scalability of “big data”.

Genomics research continues to be driven by the need to solve genetically undiagnosed cases and address the many variants of unknown significance identified in both research and diagnostic settings. In close collaboration with Dr Anthony Cheong and Dr Danqing Zhu at the Molecular Medicine Laboratory, Concord Hospital, my team at the Northcott Neuroscience Laboratory, ANZAC Research Institute has implemented research strategies to help solve the referred genetically undiagnosed cases that have undergone testing for known genes. Release of the T2T-CHM13 reference genome in 2022 and the draft pangenome reference in 2023 (phased genome haplotypes from diverse populations) has provided a “complete” human genome reference coupled with the “complete” spectrum of human species DNA variation.

By combining the improved accuracy and affordability of long read sequencing with the complete genome reference resources, our research is focusing on the neglected non-coding or “dark genome” for mutation screening unsolved cases (Figure 1). Implementing cloud-based computing in collaboration with Dr Georgina Samaha (Australian BioCommons, Sydney Informatics Hub, University of Sydney), has been critical for developing pipelines to screen non-coding DNA for pathogenic structural variation (SV) (duplications, deletions, inversions, translocations, repeat expansions). This has significantly improved the sensitivity and accuracy of SV calling and provided highly effective single-nucleotide polymorphism (SNP)/indel filtering. A recent study to identify a new dominant mutation in an unsolved family narrowed the search from ~2 million variants to 59 heterozygous SNPs and 25 candidate SVs.

As research moves forward to benefit from the advances in technology and “omics” resources, the IPM&B has been addressing the multifaceted challenges for handling the scalability of data, in the context of big data storage, transfer, and analysis, as well as securing funding for the growing bioinformatic requirements. Cloud computing is proving to be a transformative and necessary solution in which on-demand access to high performance computing will allow researchers to scale their computational infrastructure based on the specific needs of project analyses. Leveraging cloud-based infrastructures will enable researchers to focus on scientific objectives without being hindered by computational or storage limitations, ultimately accelerating discoveries and advancing the field of personalised medicine.

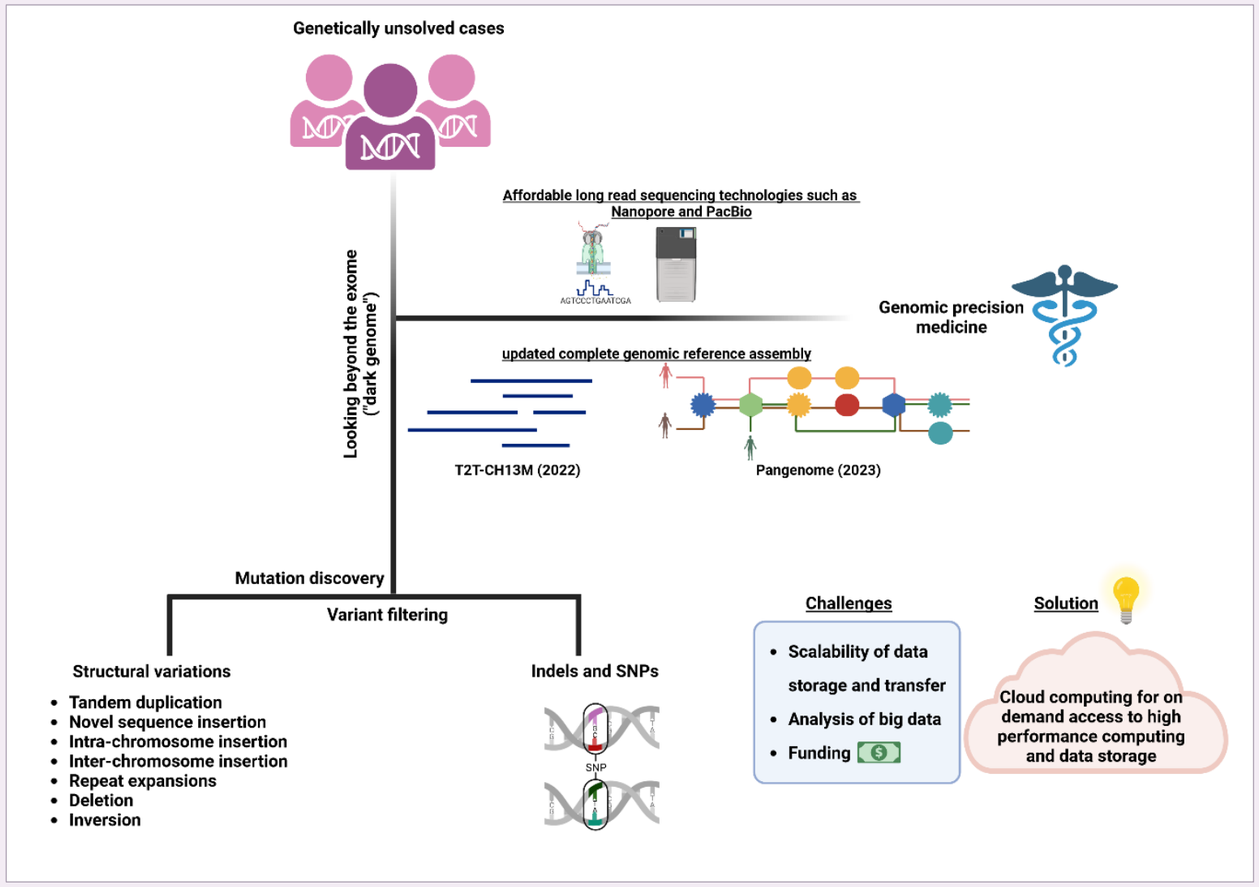

Figure 1. Framework for leveraging advances in genomics research for mutation discovery.
Acknowledgements, Dr Ramesh Narayanan (Postdoctoral Fellow, ANZAC Research Institute) for assistance with the figure.

IPM&B Research Mentoring Program

As part of introducing the IPM&B mentoring program, in 2022 and early 2023, I ran a series of mentoring workshops for a small number of clinical researchers (in medicine and nursing) focusing on the components that made up a successful MRFF grant.

To continue the mentoring program in 2024, a set of webinars will be given by either clinician researchers or basic scientist researchers with a proven research track record highlighting strategies, infrastructure, collaborations, and networks they have built up that enabled success in major grant applications.

Invitations will be issued to a large cohort of clinicians, scientists, nurses, and allied health at 5 years post-PhD or Fellowship qualification.

Once these webinars are completed, 2-3 participants will be invited to work more closely with the IPM&B in a focused 1:1 co-mentorship (having both a clinician and scientist mentor) for personal mentoring. With the expertise available in the IPM&B from clinician scientists and basic scientists, this will facilitate personal mentoring for technologies, skills, or ideas in genomics as part of their research work.

Expanding Omics Capability

Professor David Sullivan
Head, Department of Chemical Pathology, RPA Hospital

The application of the principles of precision medicine and bioinformatics at RPA Hospital has led to successful novel therapies. This is exemplified by the recent publication of clinical trials in two high-ranking journals[1, 2]. The use of anti-ANGPTL3 small interfering mRNA therapy has achieved control of cholesterol levels in previously untreatable cases on Homozygous Familial Hypercholesterolaemia which typically caused fatal heart attacks before the age of twenty. Likewise, anti-apoC3 small interfering mRNA therapy has achieved control of triglyceride (fat) levels in previously untreatable cases of Homozygous Lipoprotein Lipase deficiency where the fat build-up makes the blood look like a strawberry milkshake with the result that catastrophic attacks of acute pancreatitis occur throughout life.

The discovery of these treatment targets reflects the application of the principles of Mendelian Randomization, which is sometimes referred to as "Nature's Clinical Trail". This technique allows inferences about causality to be made from observational studies because it prospectively controls for confounding influences and reverse causality. The guiding principle of Mendelian Randomization is as follows: if the genotype and phenotype exert the same effect on the disease in question, 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. 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 other less protective drugs. Most recently, it identified Proprotein Convertase Subtilin Kexin-9 (PCSK9) as a safe and effective target for next generation cholesterol-lowering therapy and in doing so, accelerated the design and development of therapeutic innovations, illustrated by the agent "Incliseran".

The IPM&B and Department of Chemical Pathology at RPA Hospital have been involved with all these enterprises as well as others targeting a new independent risk factor, apolipoprotein (a).

It is likely that gene therapy, in the form of CRISPR-9 technology, will be used to achieve once-in-lifetime remedies for these and related conditions.

For a fully-fledged involvement in precision medicine, the IPM&B needs to fully engage with other analytical techniques and the way they integrate the other aspects of pathophysiology. The other "omics" are driven by many technologies, but possibly the leading one amongst these would be mass spectroscopy.

The Sydney Biomedical Accelerator (SBA) Synapse capability will provide a strong environment for the IPM&B to pursue these objectives with other analytical techniques and their associated "omics". The SBA will foster collaboration with scientific interests and capabilities of university sectors in a manner which encourages clinicians to interface with bioinformaticians so that, as the volumes of data generated increase, clinicians select the right path for analytical techniques, software and hardware.

The different analytical techniques and their associated "omics" naturally progress along logical pathways – genomics, provides a platform for transcriptomics, metabolomics, proteomics and so on. The whole disease processes from a genomic cause through to the metabolomic manifestation can be traced. This will provide a powerful resource for the diagnosis of rare diseases. Furthermore, it will identify the treatment targets that are most relevant for the common preventable chronic diseases which contribute the greatest burden of disease.

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Artist Impression: Sydney Biomedical Accelerator (SBA)

Sydney Biomedical Accelerator

THE UNIVERSITY OF SYDNEY | NSW GOVERNMENT | Sydney Local Health District

Precision Medicine Research Facility

A major activity in 2023 was planning for the Sydney Biomedical Accelerator (SBA), a joint University of Sydney (USYD) and Sydney Local Health District initiative, to be built behind the current Gloucester House, the old Bosch library and lecture theatres at USYD. Once funding from the NSW Government and a generous benefactor was announced, it was full speed ahead with the research complex roughly divided into four adjacent sections called "buildings" A (Gloucester House), B (to be named), C and D (Isaac Wakil building to house USYD staff). The revamped Gloucester House will include a sophisticated dry laboratory, bioinformatics, ICT focus and an innovation centre; Building B will have District research laboratories and other infrastructure complementing what is found on the same floor for USYD staff and initiatives. Through the newly formed District Internal Advisory Committee, all aspects of planning for buildings A and B were reviewed by a broadly based expert group co-chaired by the CE Dr Teresa Anderson and Dr Paul Torzillo.

The process to design new laboratories with key themes was complex and required considerable input from District health professionals, academics and researchers, facilitated by expert coordinating skills from Sydney Research's Vicky Taylor and Penny Schmidt.

Towards the end of 2023, a final addition to the SBA was supported by the District's Internal Advisory Committee. This was to develop a Precision Medicine Research Facility (PMRF) laboratory in building B. The PMRF will enable:

- development of state-of-art research applications for precision oncology within a NATA accredited laboratory, and
- future new technologies required for precision medicine with the current interest being genomic sequencing via long reads, although other omics might also be an R&D focus in this facility.

New developments within the PMRF will be NATA accredited to the highest clinical level for instant application within the SLHD clinical environment.

Research Activity

Grants awarded

- Harnessing nanopore sequencing technology to improve diagnosis of human disease. MRFF Early to Mid Career Researchers. Dr Amali Mallawaarachchi, CIC. Funding $1million
- RACP Jacquot Research Establishment Grant. Dr Amali Mallawaarachchi, CI. Funding $90,000
- Avant Early Career Research Grant Dr Alison McLean.
- Developing a long-read nanopore sequencing platform for Indigenous genomics. Genomics Health Futures Mission. Dr Amali Mallawaarachchi, CIE. Funding $1million
- Kidgen National Kidney Genomics Program Genomics Health Futures Mission Dr Amali Mallawaarachchi, CIF. Funding $3million
- Implementation of Metformin theraPy to Ease DEcline of kidney function in PKD – the IMPEDE-PKD trial. Medical Research Future Fund. Dr Amali Mallawaarachchi, CIJ Funding $2.5million
- Monogenic Parkinson's Disease Australia Initiative (MonoPDAus Initiative) - towards a precision medicine approach. Genomics Health Futures Mission. Assoc Prof Kishore Kumar, CI. Funding $2.95million
- Audit of uptake of genomic testing in Australia. Dr Felicity Collins, PI for RPA Hospital site.
- Protocol No X17-0369 Australian Genomics Health Alliance: Preparing Australia for genomic medicine. Medical Research Future Fund. Dr Felicity Collins, PI for RPA Hospital site.
- Clinical Diagnostic Research Network Medical Research Future Fund. Dr Felicity Collins, AI.
- Accelerating precision medicine for IPF: characterizing the high-risk IPF genetic landscape. Medical Research Future Fund Dr Felicity Collins, AI.
- Newborn Gen Seq Trail (Newborn Genomic Sequencing in screening: Therapy Ready And Information for Life). Medical Research Future Fund. Dr Anthony Cheong, AI.

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Our Education

Genomics Webinars

A suite of five educational webinars illustrated the utility of genomics in various clinical settings

The 2023 webinar series was planned to meet the educational needs of the IPM&B membership with target groups including specialists, trainees and early career scientists.

Compared to 2022, there was an increase in both scientific staff and trainees attending the webinars. The 2023 program also saw an increase in attendees from the Agency for Clinical Innovation, HETI and interstate hospitals. Attendees from RPA Hospital remained steady as the largest group at 37%.

Thank you to Melissa Cole, Operations Manager, for organising these activities and for providing a comprehensive overview of attendances and feedback on presentations. This input is essential to ensure that planning for 2024 aligns with the core activities of the IPM&B, which include the education of a broad range of health professionals in genetics/genomics/precision medicine and building capacity in bioinformatics skills across Sydney Local Health District.

With the growing interest in artificial intelligence (AI) for clinical applications, Dr Abdul Baten and others from the IPM&B met with Professor Adam Dunn (from the University of Sydney's Department of Biomedical Informatics and Digital Health) to discuss possible educational collaborations in AI in 2024. This would need to take into account the AI strategies already underway in Sydney Local Health District's Digital Health and Innovation Department which proposes to establish an AI Implementation Centre of Excellence - see Sydney Local Health District's Digital Health Strategy 2022-2027.

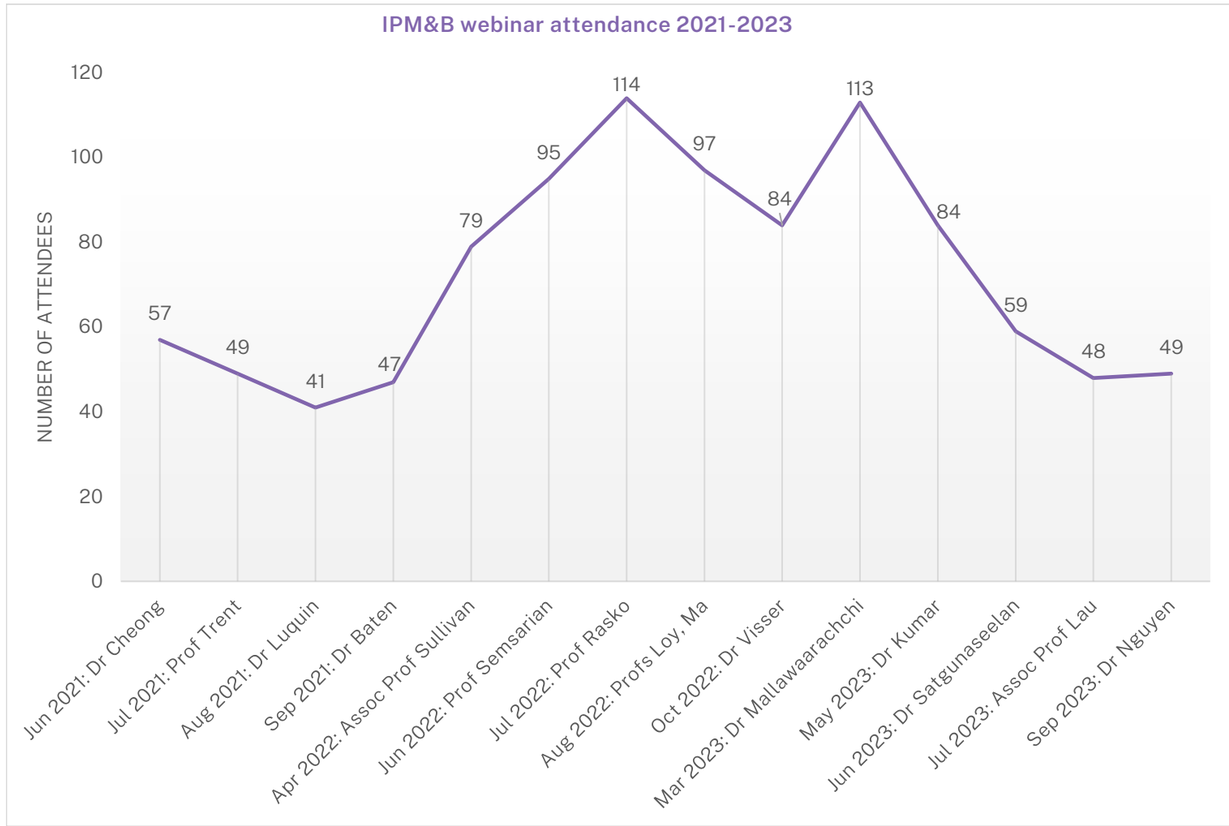
Genetic kidney disease
presented by
Dr Amali Mallawaarachchi

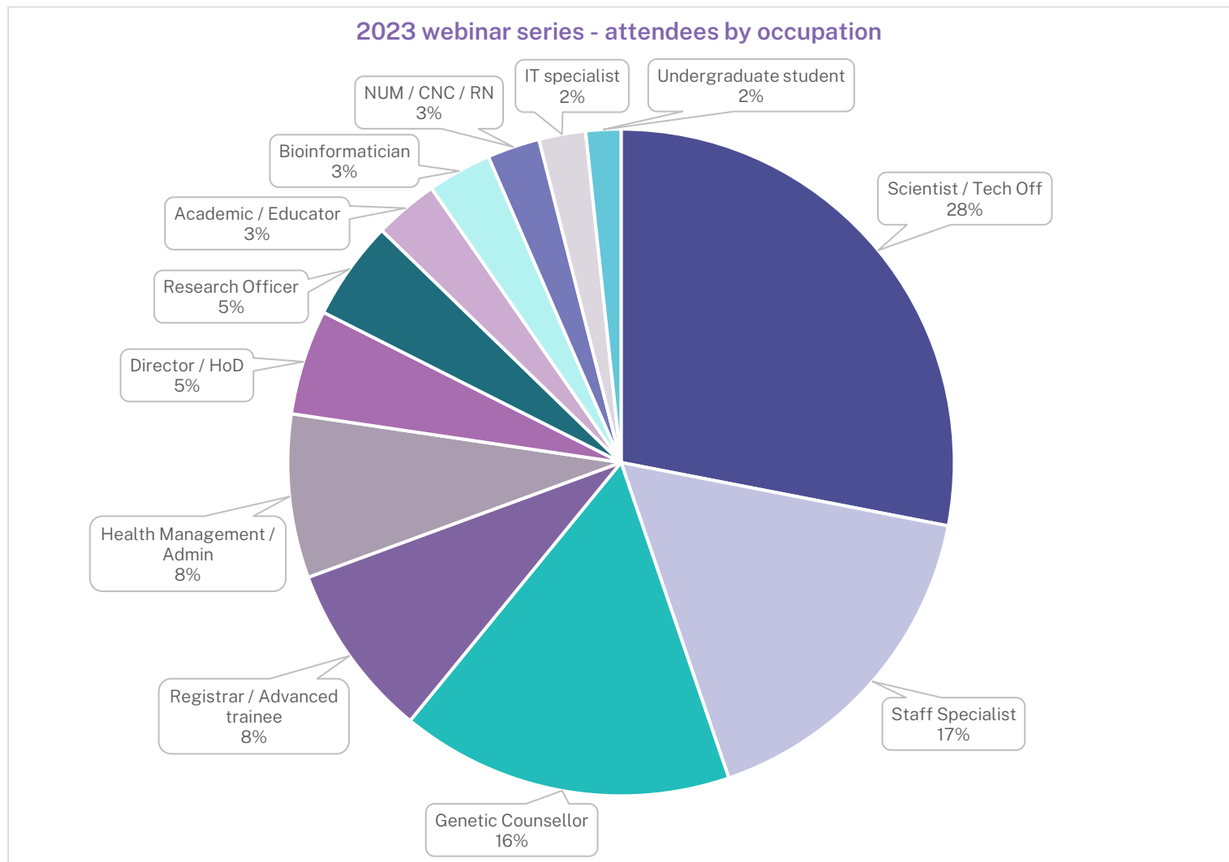
DNA repeats causing neurological disorders
presented by
Assoc Prof Kishore Kumar

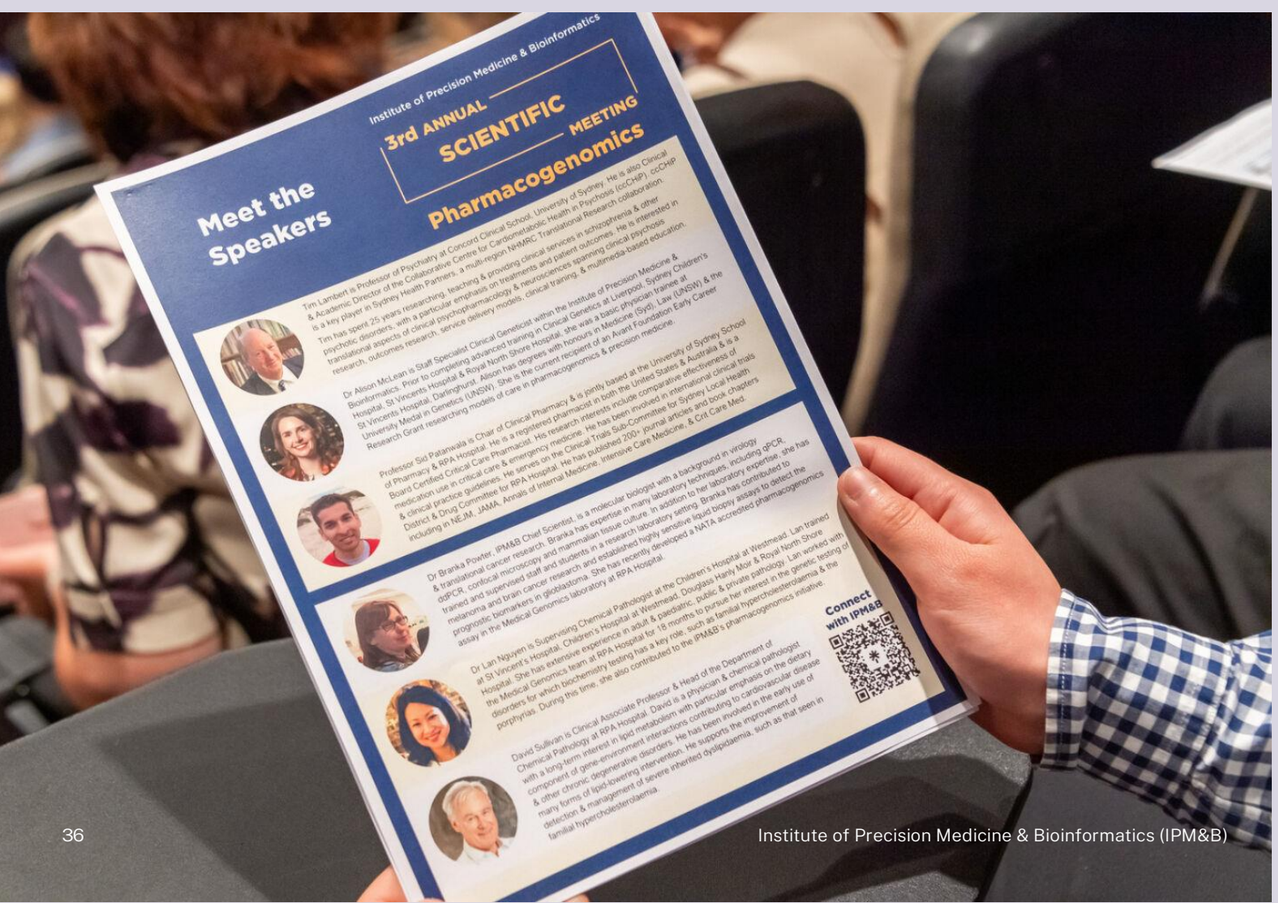
Genomics in neuropathology
presented by
Dr Laveniya Satgunaseelan

Genomics in the Pulmonary Hypertension Clinic
presented by
Assoc Prof Edmund Lau

Polygenic risk inheritance
presented by
Dr Lan Nguyen







Annual Scientific Meeting

Pharmacogenomics

The IPM&B's third Annual Scientific Meeting (ASM) with the theme of pharmacogenomics (PGx) was held on 12 October 2023 at the Kerry Packer Education Centre. The meeting was opened by our Chief Executive, Dr Teresa Anderson AM, who is a strong supporter of PGx. The ASM brought together a mix of health professionals to describe their experiences and views on development of a PGx Model of Care (MoC) for Sydney Local Health District.

The concept of PGx (the right drug for the right patient at the right time) has had limited implementation into clinical care to date (apart from a few single genetic tests funded in Australia through Medicare, like TPMT testing when using thiopurine drugs and HLA testing to avoid severe adverse reactions in treating HIV or epilepsy).

With the technological advances in genomics, it is now possible to test for the metabolising potential of many drugs which will benefit patients on polypharmacy or those taking drugs that have significant side effects. PGx comes with challenges in terms of delivering results quickly and providing clinicians with results that are clinically meaningful, so appropriate actions can be taken. Hence, the ASM was designed to seek broad input into what might be done at Sydney Local Health District when a comprehensive PGx program is rolled out.

Views were sought from experts in psychiatry, clinical genetics, pharmacy, laboratory genetics, chemical pathology and health economics. Many thanks to speakers Professor Tim Lambert, Dr Alison McLean, Professor Sid Patanwala, Dr Branka Powter, Dr Lan Nguyen, Assoc Professor David Sullivan and Assoc Professor Michelle Cunich for their informative presentations and comments.

At the ASM the following issues were highlighted:

- The value of including PGx in treating mental health disorders, particularly at the beginning of treatment, to allow a precision medicine MoC for patients who may need long term treatment.
- The importance of PGx in clinical trials and the views from health professionals on what is needed in a PGx report (which must be provided in a short turnaround time).
- The need to include in the MoC a pharmacist or pharmacologist to assess complex drug-to-drug interactions.
- The laboratory challenges, including fast turn around time, where medications need to be administered urgently.
- Therapeutic drug monitoring options to providing information on drug metabolism and excretion as well as confirming drug compliance.
- Finally, a PGx MoC would need to consider health impacts, costs and effectiveness not necessarily in large cohorts but, if used as precision medicine, on a more individual basis.

The ASM was successful in highlighting options and considerations for the development of a PGx MoC. We plan to have a comprehensive PGx program in place within five years, enabling all patients utilising health facilities within the District to have the option to be tested for a range of genes that influence drug metabolism (activation or excretion) and imbedding PGx in clinical care and research activities.

Cloud Computing Forum

Genomics & Cloud Computing at Sydney Local Health District

Cloud based resources for data storage and analysis are essential for genomics in precision medicine. This IPM&B's Genomics & Cloud Computing Forum held on 15 August 2023 looked into the current clinical and research applications of cloud computing in genomics within Sydney Local Health District, plus cybersecurity requirements and how precision medicine may be advanced by machine learning and artificial intelligence.

For those working with large data sets, and in the context of precision medicine, that would be genomics, we are moving towards cloud computing as local servers with computing power for analysis and storage are phased out. Cloud computing is essentially a commercially available server located off-site (preferably in Australia) that can provide the computational power for analysis and storage of data. Two popular commercial providers are Amazon (AWS Cloud) and Microsoft (Azure Cloud).

With growing eHealth initiatives underway, cloud computing has become integral to many of our clinical service activities. For analysis and storage of large data sets measured in petabytes, we have become totally reliant on the cloud. Consequences of this ongoing transition are significant: greater cybersecurity awareness and compliance requirements; increasing reliance on sophisticated ICT support for a range of software programs that require constant monitoring, upgrading and security assessments.

The IPM&B will need to be vigilant to address the demands of cloud computing to ensure that clinical service and research work in genomics, and at some future date other omics, are not compromised.

In parallel with these changes is the expanding interest in artificial intelligence and machine learning. A participant at the Forum asked for more information about these developments in clinical medicine and research, and the IPM&B will focus on these aspects in future education sessions.

The Forum was chaired by Prof Sebastiaan van Hal (Infectious Diseases and Microbiology, RPA Hospital) and included the following presentations:

- Dr Anthony Cheong: Interpretation of inherited panel & WES using SOPHiA DDM™
- Associate Professor Bing Yu: Application of cloud computing in somatic cell DNA and RNA testing
- Dr Hugh French: Developing long read sequencing solutions in clinical diagnostics
- David Norwood: Cybersecurity
- Dr Abdul Baten: Advancing precision medicine using machine learning and AI.

The IPM&B is liaising with the University of Sydney's Biomedical Informatics & Digital Health group to discuss this important area of interest further.

Our Organisation

Our Executive Leadership Team

Professor Ron Trent

PhD, MB BS, BSc(Med) (Sydney), DPhil (Oxon), FRACP, FRCPA, FFSc, FTSE

Director

Ron is Head of the Department of Medical Genomics at RPA Hospital and Director of the Institute of Precision Medicine & Bioinformatics. He brings to the Institute considerable experience from his 12 years on NHMRC principal committees including Council, Research Committee and Chair of the Human Genetics Advisory Committee. He was a Director for the Garvan Institute of Medical Research from 1998-2009 and was recently re-appointed for another triennium. In 1991, he became the Foundation Professor of Medical Molecular Genetics at the University of Sydney. He has a strong interest in medical education and published his book Molecular Medicine in 1993, with a 4th edition in 2012. In 1996 he developed a training course leading to Fellowship in Genetic Pathology in the Royal College of Pathologists of Australasia. This program provided, for the first time, an opportunity for medical graduates to pursue a career in laboratory genetics.

Professor Marina Kennerson

BSc(Hons); MSc(Med); PhD

Deputy Director

Marina is Director of the Northcott Neuroscience Laboratory at the ANZAC Research Institute, Principal Scientist with the Molecular Medicine Laboratory at Concord Hospital and Senior Principal Research Fellow with the Sydney Medical School, University of Sydney. She is a key international researcher in the field of hereditary neuropathies and has developed the genomics gene discovery and translational program at the ANZAC Research Institute. She is a member of the international CMT and Related Neuropathies Consortium Board, Chair of the Asian Oceanic Inherited Neuropathy Consortium, and member of the Scientific Advisory Board for the CMT Research Foundation. Professor Kennerson has discovered several neuropathy genes including ATP7A and PDK3 as well as structural variation mutations causing gene dysregulation as a new disease mechanism for hereditary neuropathies. Professor Kennerson is recognised for teaching gene mapping linkage analysis both locally and internationally and is the Genetics Unit of Study Co-ordinator for the Masters Course at the Brain and Mind Centre.

Professor Clement Loy

BA, MB BS, MMed(Clin Epi), FRACP, PhD

Deputy Director

Clement is Head of the Macquarie Medical School and Dean of Medicine for the Faculty of Medicine, Health and Human Sciences, Macquarie University. He 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 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 first-authored review in the Lancet (2014). He serves the wider community as a member of the Pharmaceutical Benefits Advisory Committee.

Dr Branka Powter

BMedSci(Hons), PhD, GradDip(Education)

Chief Scientist

Branka is a molecular biologist with a background in virology and translational cancer research. She has expertise in extraction of nucleic acids from various sources, PCR, ddPCR, confocal microscopy and tissue culture. Branka has contributed to melanoma and brain cancer research and established highly sensitive liquid biopsy assays to detect the prognostic biomarkers in glioblastoma. She was also instrumental in the development of pharmacogenomics testing at RPA Hospital. Branka has extensive experience in laboratory supervision of Honours, ILP and PhD students and has co-authored a range of publications. Her scientific interests are wide ranging and include virology, genetics and pharmacogenomics.

Melissa Cole

BAppSci (Information)

Operations Manager

Melissa has managed the operations of the Institute since it was established in 2020. Her role is varied and includes staff administration, recruitment and onboarding, procurement, financial reporting, event management, media and communication strategies. She is also the secretary for the Institute's Executive Leadership Team and Strategic Advisory Council. She enjoys facilitating collaborations for the IPM&B membership. Melissa moved into health administration following a 20-year career in legal and business publishing. She has extensive experience in business communication, administration, marketing, public relations, and project management.

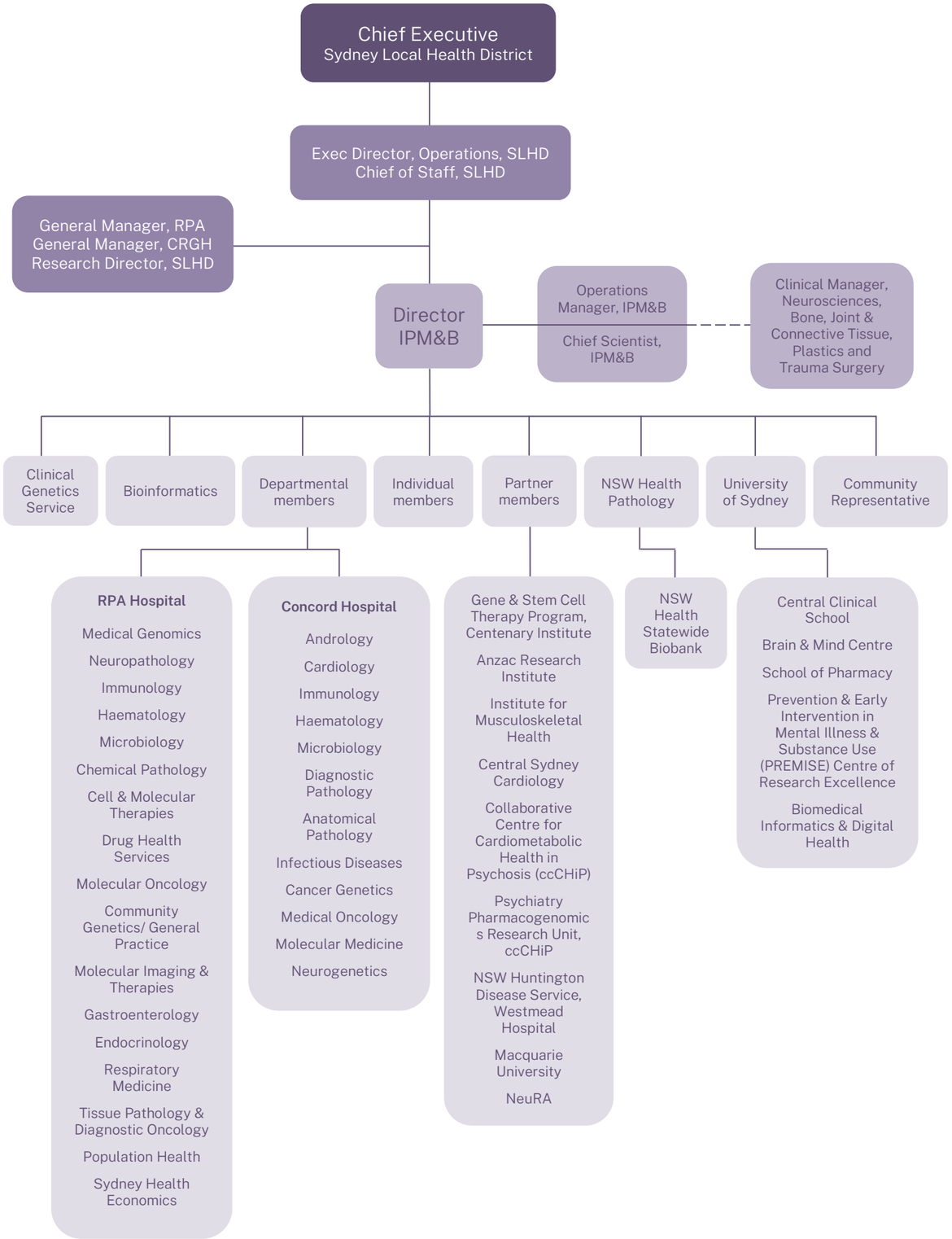
Dr Alan McPhail

B AppSc, MEngSc, PhD

Consumer Representative

Alan's final appointment prior to his retirement in 2012 was as Dean of the School of Engineering and Built Environment, Central Queensland University. He previously taught at CQUniversity Sydney and coordinated courses in computing systems and data communications. He also developed CQUniversity's Master of Management (Engineering). Earlier in his career, he served his apprenticeship as a communications technician in the Royal Australian Navy. Following his retirement, Alan volunteered at Concord Hospital and now gives his time, expertise and ideas to a number of peak committees across Sydney Local Health District as a consumer representative. Alan has a particular interest in consumer and community involvement in research, advocating to ensure research results are communicated in a way that is understandable to the wider community.

Our Governance



Strategic Advisory Council

In 2023, the previous IPM&B Management Committee was realigned into a Strategic Advisory Council. Quarterly meetings of the Council were targeted to provide high level advice on significant matters for the IPM&B in keeping with our vision to ensure the benefits of precision medicine are rapidly and effectively implemented into the clinical care of patients and their families.

Executive Leadership Team, IPM&B
Professor Ron Trent
Professor Marina Kennerson
Professor Clement Loy
Dr Branka Powter
Melissa Cole
Dr Alan McPhail

Clinical Genetics Service, IPM&B
Dr Felicity Collins

Bioinformatics, IPM&B
Dr Abdul Baten

Research Director, SLHD
Professor Warwick Britton

Head, Central Clinical School
Faculty of Medicine and Health
University of Sydney
Professor Stephen Twigg

Director, Collaborative Centre for Cardiometabolic Health in Psychosis
Professor Tim Lambert

Head, Department of Cell and Molecular Therapies
RPA Hospital
Professor John Rasko

Head, Department of Chemical Pathology
RPA Hospital
Clinical Associate Professor David Sullivan

Professor of Allied Health (Community Health)
SLHD
Professor Andrew Baillie

Head, Somatic Cancer Testing Service
Department of Medical Genomics
RPA Hospital
Associate Professor Bing Yu

Head, Department of Immunology
RPA Hospital
Associate Professor Stephen Adelstein

Head, Department of Diagnostic Pathology
Concord Hospital
Dr Margaret Janu

Senior Staff Specialist in Haematology
RPA Hospital
Professor Harry Iland

Senior Staff Specialist in Infectious Diseases & Microbiology, RPA Hospital
Professor Sebastiaan Van Hal

Senior Staff Specialist in Respiratory Medicine
RPA Hospital
Associate Professor Edmund Lau

Staff Specialist in Molecular Medicine
Concord Hospital
Associate Professor Kishore Kumar

Staff Specialist in Haematology
Concord Hospital
Dr Vivien Chen

Staff Specialist in Cardiology
RPA Hospital
Dr Elizabeth Robertson

Staff Specialist in Genetic Pathology
IPM&B
Dr Anthony Cheong

Director of Biobanking
NSW Health Statewide Biobank
Professor Jennifer Byrne

Senior Operations Manager
NSW Health Pathology
Bobby Dimitrijovski

Financial Report

2022-23 Financial Year

Since establishment in early 2020, the IPM&B operated from a single cost centre. To enable the separation of activity areas and more effective long-term planning, the IPM&B worked with District Finance during 2022 to establish additional activity-based cost centres. Transfers to align IPM&B staff under the appropriate activity-based cost centre were completed in late 2022.

The below snapshot represents combined expenditure and revenue across all IPM&B cost centres. Approximately $2.5 million was employee-related expenses and a further $74,329 went towards Visiting Medical Officers (VMOs). Other operating expenses, including genetic testing sent to external laboratories, consumables, equipment repairs and replacement totaled $226,383. Our own-source revenue included $19,622 from patient fees.

Actual expenses	**$**	**%**
Employee Related	$2,498,793	89.26%
VMOs	$74,329	2.66%
Goods & Services	$202,942	7.25%
Repairs, Maintenance & Renewals	$23,441	0.84%
Total Expenses	**$2,799,505**	**100.0%**

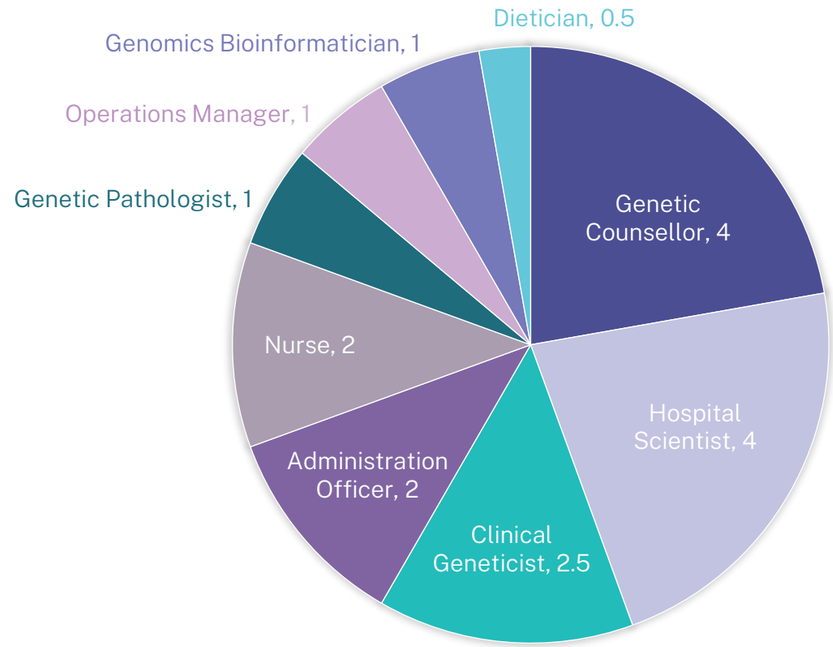
Actual revenue	**$**	**%**
Patient fees	$19,622	100.0%
Net Cost of Services	**$2,779,883**	**100.0%**

Government contributions	**$**	**%**
Crown Acceptance	$87,636	100.0%
Year Total Result	**$2,692,247**	**100.0%**

Source: Sydney Local Health District Year Total Financial Reports the year ended 30 June 2023.

Our Staff

Administered staff — FTE profile



2023 Total FTE: 18

New appointments

IPM&B Deputy Director Professor Clement Loy was appointed as Head of the Macquarie Medical School and Dean of Medicine for the Faculty of Medicine, Health and Human Sciences, Macquarie University. Clement remains Deputy Director of the IPM&B and continues collaborative research initiatives.

Dr Alison McLean joined the Institute of Precision Medicine & Bioinformatics as a Clinical Geneticist in the Clinical Genetics Service. Dr McLean is the current recipient of an Avant Foundation Early Career Research Grant researching models of care in pharmacogenomics and precision medicine.

Alison completed advanced training in Clinical Genetics at Liverpool, Sydney Children's Hospital, St Vincents Hospital and Royal North Shore Hospital.

Previously she was a basic physician trainee at St Vincents Hospital, Darlinghurst. Alison has degrees with honours in Medicine (Syd), Law (UNSW) and the University Medal in Genetics (UNSW).

Future Directions

Professor Ron Trent
Director, IPM&B

Apart from core activities around IPM&B administration and governance, particularly the ongoing consolidation of the various costs centres and their budgets, a key focus for the IPM&B will remain cloud computing and related to this is artificial intelligence (AI). This is necessary since work in precision medicine that requires “omics” capability will generate very large data sets requiring storage and analysis.

The traditional approach using local servers will no longer be available as eHealth initiatives push more health-related matters onto the cloud with its unlimited capacity. However, this also means more stringent requirements for compliance around cybersecurity particularly within a health environment. Therefore, a key role of the IPM&B must be to work with relevant partners, particularly Digital Health & Innovation at Sydney Local Health District to enable precision medicine to proceed and expand within the digital infrastructure required.

There is extensive digital and bioinformatics infrastructure already available at the University of Sydney for its sophisticated research requirements. However, are these resources cybersecure for research and clinical care initiatives within the hospital environment? There are state-wide genomics bioinformatics and digital health infrastructure being built through NSW Health Pathology, but how do these address research and clinical care initiatives at Sydney Local Health District? There is potential for the IPM&B to help navigate this complex milieu to benefit all aspects of precision medicine within the District.

The potential for AI was highlighted many times during 2023 with governments in Australia and overseas encouraged to become pro-active to harness the benefits while minimising the risks. Sydney Local Health District is showing leadership through its Digital Health & Innovation strategies for AI. AI will impact on precision medicine when sophisticated decision making will be required to assess data generated from genomics, transcriptomics and in other omics testing.

Apart from the practical benefits of AI, there are also the educational issues that need to provide the background and understanding for this fascinating development in clinical medicine. The IPM&B will collaborate with the Institute of Academic Medicine, University of Sydney and the District’s Digital Health & Innovation team to ensure the District’s precision medicine workforce is AI “compliant”.

Finally, an important development in 2023 was the launch of the IPM&B’s internet site. For this we can thank IPM&B Operations Manager Melissa Cole, who worked closely with the Corryn McKay’s Strategic Relations and Communication team, to be one of the first groups within the District to adopt the new website content management system. This was an important step as our previous intranet site was available only to those working within health. The importance of communication in the modern era continues to grow and, in particular, social media platforms that are pervasive yet also a risk within the sensitive health environment. During 2024 the IPM&B’s internet will be enhanced to provide further news and resources in precision medicine.

Our Stories

Key challenges of AI and bioinformatics in the era of precision medicine

Dr Abdul Baten, Genomics Bioinformatician
IPM&B

Bioinformatics plays a critical role for analysing and interpreting large-scale biological data, leading to insights into fundamental biological processes, disease mechanisms and personalised medicine. By leveraging computational and data-driven approaches, bioinformatics helps to integrate and analyse large-scale genomic, proteomic and clinical data to identify disease subtypes, biomarkers and potential therapeutic targets. As the field of bioinformatics continues to evolve, it is expected to play an increasingly critical role in advancing our understanding in many areas of life science and more importantly, improving human health through precision medicine.

Artificial intelligence (AI) and machine learning (ML) based methods have had a significant impact on bioinformatics in recent years and are continuing to evolve. AI and ML based algorithms have enabled the analysis of large-scale biomedical data, systems biology, protein structure, the development of precision diagnosis, predictive modelling of disease risk and treatment response, accelerated drug discovery by identifying potential drug targets and predicting efficacy of new drugs.

Though AI and ML is playing an increasingly critical role in bioinformatics, there are some critical challenges that need to be addressed.

Data integration

In the era of precision medicine, the challenge of integrating data from multiple sources arises due to the complexity and diversity of data types. For instance, genomics, transcriptomics and proteomics data are stored in different databases and file formats, making it difficult to merge them into a single dataset. Additionally, clinical data from electronic health records also need to be integrated with omics data to provide a holistic view of the patient's health status.

AI algorithms can aid in the integration of these diverse data types by automatically extracting relevant information and mapping it to a unified ontology or schema. However, challenges remain in ensuring the quality and consistency of data across various sources.

Computational power

The large volumes of data generated by high-throughput sequencing technologies require significant computational power to process and analyse. Traditional computing infrastructures may not have the capability to handle the size of these datasets, which has led to the development of cloud-based computing solutions and distributed computing infrastructures. These systems can provide access to shared resources and enable parallel processing to speed up analysis times. Nevertheless, challenges remain in the efficient utilisation of computing resources, particularly in terms of optimising algorithms for parallel processing, access and security of cloud computing resources.

Data quality

The accuracy and completeness of data are crucial factors in precision medicine, as they can impact the reliability of analysis and the validity of diagnoses. Therefore, it is essential to ensure the quality of data through quality control measures, standardisation of data formats, and the use of standardised protocols for data collection and processing. Additionally, AI algorithms can aid in the identification and correction of errors in the data, but it is essential to validate the results and ensure they are biologically meaningful.

Interpreting biological significance

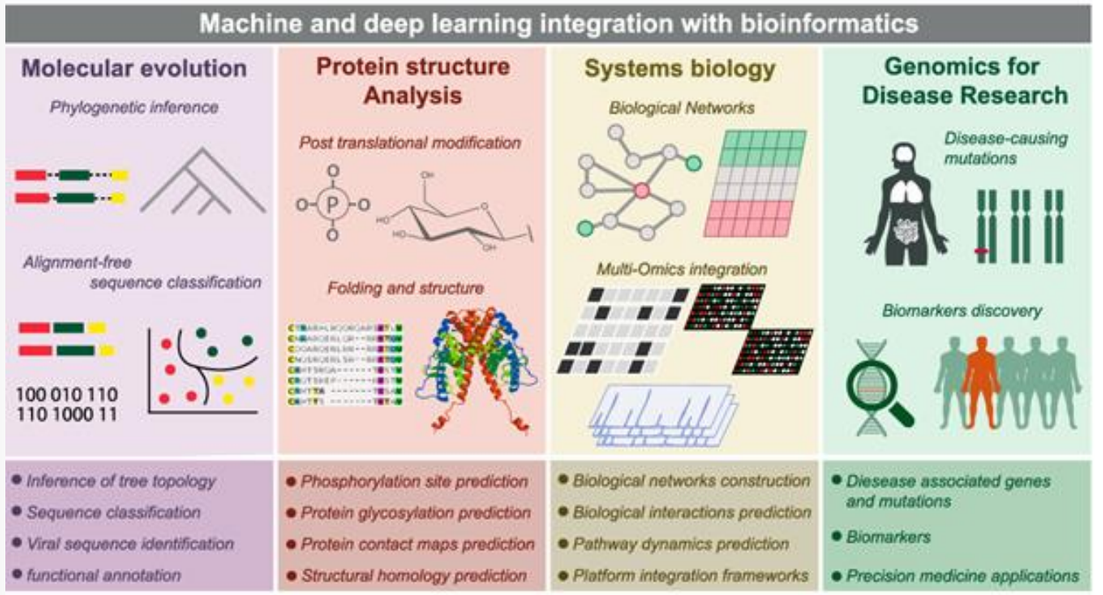
The challenge of interpreting the biological significance of results obtained from large-scale genomic and other omics datasets is a critical issue in precision medicine. AI algorithms can help identify patterns and relationships in the data, but it is still challenging to translate these into actionable insights for clinical decision making.

Interpretation of results requires a thorough understanding of the underlying biology, as well as the context in which the data was collected. Therefore, it is essential to involve experts from multiple domains, including bioinformatics, genetics, and clinical medicine, in the analysis and interpretation of results.

Ethical and legal issues

The use of AI in precision medicine raises several ethical and legal concerns related to data privacy, patient consent, and bias. For instance, there is a risk of exposing sensitive patient information during data sharing and analysis, which may violate privacy regulations.

Additionally, there is a need to ensure that patients provide informed consent for the use of their data in research, and that the data is de-identified to prevent identification of individuals. Furthermore, bias in AI algorithms can result in unequal treatment and discrimination, which can have significant implications for patient care. Therefore, it is essential to establish ethical guidelines and regulations to ensure that the use of AI in precision medicine is safe, fair, and transparent.



Applications of integrated machine learning techniques with bioinformatics (Source: 10.3390/ijms22062903)

Our Stories

2023 Genomics Landscape

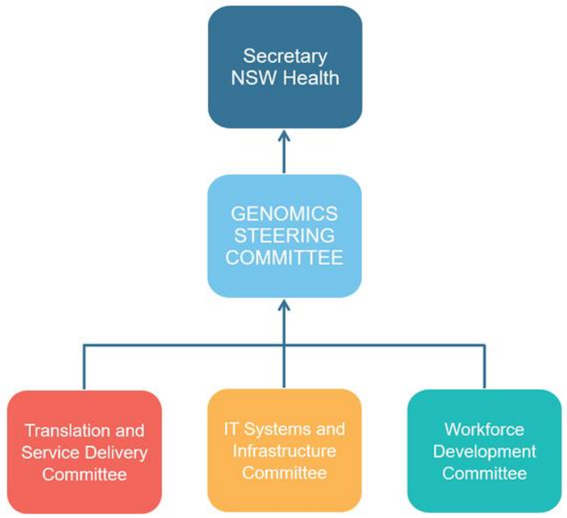
Professor Ron Trent, Director, IPM&B

Genetics (the focus here is on one to a few protein-coding genes) has evolved to genomics ("omics" is used to describe the concept of "many". In this case, many genes including up to all the ~22,000 genes found in humans). The next big leap forward will be sorting out the clinical significance of the non-gene containing region of the genome. This will be a massive challenge as protein-coding genes only comprise 1-2% of the genome. Once the non-coding region is understood, our knowledge of complex inheritance, for example multifactorial inheritance, where genes and the environment appear both to be playing a role in pathogenesis, will be very different to what we think we know now.

The excitement around genomics has captured the imagination of governments. Since COVID-19, the community is also well versed in what genomic sequencing means, as during the pandemic regular bulletins emerged identifying new variants or outbreaks based on changes in the sequence of viral genomes.

The NSW Health Genomics Strategy was published in June 2017. It described a broad vision of how genomics should evolve if "the promise of precision medicine and personalised care were to be fully realised". It is relatively easy to publish documents on a range of visions and directions but often goals are only achievable if there is a clear way forward, i.e. an implementation strategy.

The NSW Health Ministry took the Genomics Strategy document seriously and followed it with the NSW Health Genomics Strategy Implementation Plan 2018-2020 and now the NSW Health Genomics Strategy Implementation Plan 2021-2025. The coordination of the implementation plans is undertaken via a Genomics Steering Committee co-chaired by a senior member of the executive, a Deputy Secretary from the Ministry of Health and related working committees.



The focus of the Translation and Service Delivery Committee is on how genomic advances are incorporated into new and existing pathways for disease prevention and management. Priorities include:

- supporting equitable services, particularly across regional, rural and remote areas
- expediting translation of innovations into the NSW public health system.

The focus of the IT Systems and Infrastructure Committee is on enabling systems and infrastructure to support access and integration of workflows for clinical genomics that meet consumer needs and expectations. Priorities include:

- developing an integrated NSW genomics infrastructure model
- facilitating the ordering, tracking, reporting of genomic results and digital consent for ordering.

The focus of the Workforce Development Committee is on delivering a health workforce with improved knowledge, skills and capabilities for clinical genomics in patient care. Priorities include:

- improving point of care access to genomics education for the health workforce
- upskilling the workforce to use clinical genomics applications.

The Genomics Steering Committee is tasked with assisting the three working committees, noting the national developments in genomics and ensuring a suitable communication and implementation strategy.

The priorities noted above should be considered by the IPM&B to benchmark against what is being rolled out across NSW and so ensure that Sydney Local Health District continues its leadership role in genomics for clinical care and research.

The Genomics NSW service delivery consultation – Final Report was published on 11 January 2023. This work was commissioned by NSW Health to understand the current state of genomics mainstreaming in NSW and identify key opportunities to ensure the consistent, effective and equitable implementation of genomics across the state.

The work carried out by the Nous Group consultants involved engagement with clinicians across NSW through an online survey, followed by eight targeted consultations. The report describes six ways to support the mainstreaming of genomics in NSW:

1. **A stepped approach**: Services to grow mainstream use of genomics should take a stepwise approach recognising the critical value of existing genomic services.
2. **Patient and family centred**: Services need to remain patient and family centred and responsive to the diverse population needs and genomics literacy.
3. **Workforce support**: Non genomic and genomic clinicians need to be proactively supported to increase use of genomics.
4. **Adaptable operations**: Services must adapt to operational implications of mainstreaming genomics with regard to organisation design, processes and funding.
5. **Sustainable enablers**: Digital enablers are critical for equitable access and supporting the workforce.
6. **Research interface**: Services can enable mainstreaming of genomics through interfaces with research.

The report comes in response to the rapid expansion of genomics into all medical disciplines, and the increasing use of genomics-based strategies for clinical care, clinical trials and research.

The IPM&B's Clinical Genetics Service is available as required for consultation and assessment of genetics and genomics scenarios for diagnostic, prenatal or predictive testing. However, it is also expected that clinicians will work to improve their knowledge of genomics so that its integration into their clinical and research activities can progress efficiently for the benefit of patients and families. Gaps in genomics knowledge will need to be filled with appropriate support and consultation with genomic specialists (clinical and laboratory) when required, or as more complex genomics scenarios emerge.

The NOUS report provides a stepwise approach with various mainstreaming scenarios to show how non-genomics experts are initially engaged with relatively straightforward genomic scenarios. As the complexity increases, so does the level of genomics expertise required from the multidisciplinary team meetings to a formal referral for clinical genomics assessment. Complexity includes indications for ordering, what test to order, the consent process, understanding what genomics testing provides or cannot provide and who pays, challenges in relating phenotypes to genotypes and what the test result means.

Without mainstreaming, the medical subspecialties risk becoming less competitive with research proposals, and as the MBS continues to expand the genomics tests funded by Medicare, the specialist who does not engage in genomics may be left behind in what is a rapidly evolving precision medicine landscape.

Our Stories

Retrospective: Platinum anniversary of the DNA double helix discovery

Dr Branka Powter, Chief Scientist, IPM&B

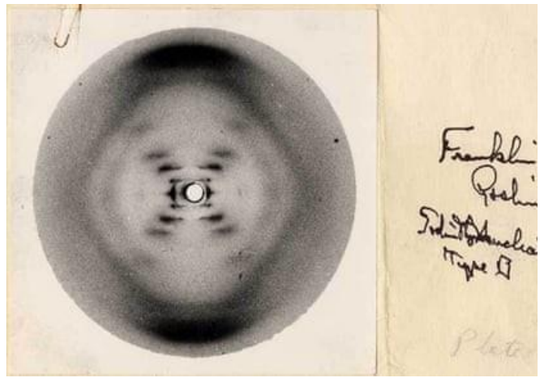
2023 marks the 70th anniversary of the discovery of the DNA structure, and it's amazing how much we have achieved since that significant event in the biological sciences. Traditionally, we celebrate James Watson and Francis Crick for their discovery of the double helix for which they were awarded the Nobel Prize (together with Maurice Wilkins) in Physiology or Medicine in 1962.

However, the discovery of the structure of DNA was made possible by the X-ray diffraction work by Rosalind Franklin (pictured) at King's College, London. It was here that her graduate student Raymond Gosling took the famous Photograph 51 image (first published in Nature 1953), which shows sodium deoxyribose nuclease from calf thymus, an image that Watson and Crick used to build the first model of DNA molecules.

Rosalind Franklin's contribution was very important towards the discovery of the double helix. She differentiated the A and B forms of DNA structure, determined that the DNA unit cell was large, and the C2 symmetry of the DNA cell unit. Rosalind Franklin also independently comprehended that DNA could specify proteins.

The anniversary of the DNA structure discovery coincides with the 20th anniversary of the completion of the Human Genome Project, which began in 1990. Not only has the Human Genome Project brought about collaboration between scientists world-wide, but it has also provided much needed publicly available data for scientists to advance the field of genomics and make significant advances in DNA sequencing technology.

With these discoveries, and the past two centuries of research in genetics and molecular biology, we have a much better understanding of the genome, genes and how the human body works. It's not hard to see how these discoveries have directly contributed to precision medicine research and development today, and how they have been beneficial in modern medicine. (Image credits: Science Source/SPL.)



Real-time R&D: Somatic Cancer

MET exon 14 skipping testing now available at RPA Hospital

Assoc Professor Bing Yu, Head of Somatic Cancer Testing Service

An innovative workflow in the RPA Hospital Medical Genomics Department has enabled the seamless delivery of combined DNA and RNA testing for MET exon 14 skipping without extending turnaround time for critical results or requiring additional tissue.

MET exon 14 skipping (METex14sk) is an important driver mutation in non-small cell lung cancer (NSCLC), occurring in 3-5% of all NSCLC. With the introduction of an MBS item in November 2022 for METex14sk testing in locally advanced or metastatic NSCLC, referrer demand for this test has significantly increased. The RPA Hospital Somatic Cancer Testing Service, led by Associate Professor Bing Yu, has developed an innovative workflow that combines both DNA and RNA-based testing on the same sample to detect METex14sk with high confidence and a rapid turnaround time.

Since January 2023, the Somatic Cell DNA Testing Service has routinely tested all lung cancer samples using a next generation sequencing (NGS) 20 gene panel, which includes multiple regions in clinically relevant target genes, such as BRAF, EGFR, ERBB2, KRAS and MET. This DNA-based NGS testing can detect genetic variants in protein coding regions (the parts of DNA that provide the instructions for how to make proteins); as well as those in selected intronic regions (in the parts of DNA previously thought of as "junk", but now recognised as important regulators of our genome). A number of these intronic variants can affect splicing – in other words, they can determine how parts of our messenger RNA are stitched together when they are copied from the DNA instructions in our genetic code. If possible splicing variants are detected, rare or unusual changes can then be confirmed using RNA-based testing. In the case of the MET gene, this involves direct RNA detection of exons 13 and 15 stitched together with exon 14 skipped.

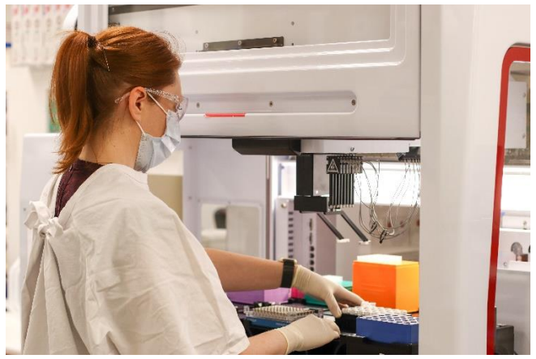
Standard workflows rely on sequential reflex testing, with the time-consuming RNA extraction, sample preparation, and sequencing occurring only after a positive DNA result is returned. The Somatic Cancer Testing Service has instead developed an automated tandem DNA and RNA extraction protocol, which is now used for all lung cancer samples to reduce sample preparation time. This means that positive DNA results can immediately reflex to RNA testing without any delay, even while the dry lab analyses and reports are still being completed.

Using a specialised in-house assay, the pre-prepared RNA can undergo confirmatory testing for METex14sk within hours of receiving positive DNA sequencing results. Designed and optimised by Associate Professor Yu and his team, this test relies on digital droplet PCR (ddPCR) technology, a fluorescent probe-based test which delivers highly sensitive (measuring down to just 5 copies of the skipping transcript) and specific results within just 4-6 hours. This rapid assay has been incorporated into the standard workflow for somatic cancer testing without extending turnaround time, allowing for timely delivery of critical results to patients and their referrers. So far, the workflow has confirmed METex14sk in 6 samples, enabling these patients to access targeted therapies on the PBS. This novel ddPCR test will be submitted to NATA for accreditation later this year.

Our Stories

NATA accreditation

Professor Ron Trent, Director, IPM&B



On 14 August, the laboratory service for the RPA Department of Medical Genomics was visited by the accrediting body NATA. This led to important new tests getting the ISO15189-RCPA stamp of approval, including pharmacogenomics and RNA based fusion gene tests, which have recently become an important focus for somatic cell precision cancer testing. Preparation for this visit was more difficult than past visits and I am very grateful for all staff members who were able to prepare the relevant documents to satisfy the accreditation requirements.

The work was led by Stuart Cole, Laboratory Manager, and I am sure Stuart is relieved that the next visit will be in four years' time. NATA accreditation is a major undertaking in any clinical laboratory, and it is something that research laboratories (for example the laboratories being designed for the Sydney Biomedical Accelerator) are starting to consider. The benefits for the latter include a more robust quality system to ensure results are of the highest standard, and information generated can be used for clinical purposes as well as research.

Hereditary Haemorrhagic Telangiectasia: New Multidisciplinary Clinic established at RPA Hospital

Kathleen Le Marquand, Senior Genetic Counsellor Clinical Genetics Service, IPM&B

Until recently, service delivery for Hereditary Haemorrhagic Telangiectasia (HHT) patients in NSW has been limited and scattered. Patients with a clinical presentation of HHT or suspected HHT were referred to clinical genetics within their area health service and often waited months for an appointment and genetic testing. Associate Professor Edmund Lau (Senior Staff Specialist in Respiratory Medicine), and Associate Professor Hubert Low (ENT Surgeon), saw the need for a HHT Clinic to make it easier for patients, as they were sharing many patients across different locations. To improve the patient journey for individuals affected with HHT, a Multidisciplinary Clinic (MDC) was proposed and discussed amongst the specialist groups.

In good news, the first and only clinic in NSW to specifically treat HHT patients has now been initiated at RPA Hospital, with the first clinic held on 28 April 2023 and subsequent clinics to be held every two months. The clinic includes Associate Professor Edmund Lau, Associate Professor Hubert Low, Kathleen Le Marquand (IPM&B Senior Genetic Counsellor), Dr Anthony Cheong (IPM&B Genetic Pathologist) and Sonia Di Lorenzo (Clinic Nurse Coordinator). This is a great opportunity to develop a statewide HHT service, considering the ability to access specialist and interventional services at RPA Hospital.

This is a new model for a genetic MDC – the clinical diagnosis is by the respiratory and ENT specialists and genetic input is from a genetic counsellor for pre and post-test counselling and family cascade testing, which is important for HHT families.

Dr Anthony Cheong has set up gene testing for HHT in the Medical Genomics Laboratory at RPA Hospital, keeping testing in-house. Clinical Geneticists are available to provide input for complex results and for patients with overlapping phenotypes, but do not attend the clinic.

There is an increasing demand for genetic counselling services across different specialty areas and trying this new model for the provision of genetic counselling services is a welcome opportunity.

New Precision Medicine Consumer Group

Melissa Cole, Operations Manager, IPM&B

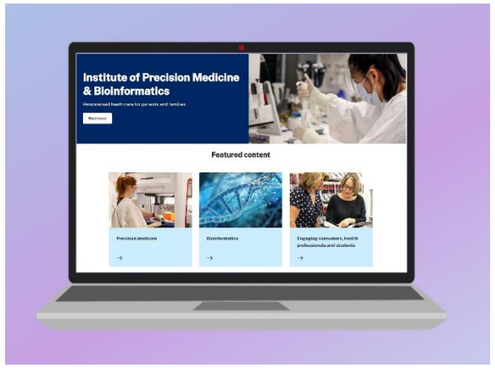
On 11 May 2023, a group of Sydney Local Health District consumer representatives and volunteers were welcomed to the IPM&B's first Consumer Engagement in Precision Medicine Workshop. The goal was to provide an opportunity for health consumers and community members to meet, mingle and learn about precision medicine and its application at Sydney Local Health District.

IPM&B Consumer Representative Dr Alan McPhail shared his experience of involvement in health research and outlined the support and mentoring available for consumers interested in getting involved. The group also heard insights from IPM&B Director, Professor Ron Trent and Sydney Health Partners Research Director, Associate Professor Angela Todd.

The group will continue to meet quarterly and IPM&B members are welcome to contact us if they would like consumer input into a research project or feedback on a new model of care.

New IPM&B website launched

Melissa Cole, Operations Manager, IPM&B



We are live! Interested to learn more about IPM&B models of care, activities and collaborators?

Check out our new website for details of our work in precision medicine and bioinformatics, plus all the latest IPM&B news, publications and upcoming events.

As part of our education initiative, we have included a Genomics Resource Library featuring recordings of all previous IPM&B webinars.

Our Stories

The evolution of Pharmacogenomics: to taste or not to taste

Dr Branka Powter, Chief Scientist, IPM&B

Many discoveries over the past century led to the science of pharmacogenomics as we know it today. One of these discoveries occurred in 1932, when a chemist named Arthur Fox determined that some individuals are unable to sense the bitter taste of phenylthiocarbamide (PTC).

The story goes that when Fox was pouring some powdered PTC into a bottle at his work bench, some of the powder accidentally blew into the air.

A colleague standing close by complained that the dust tasted bitter, but Fox had tasted nothing at all. Curious as to their different responses, they decided to taste the powder again – with the same result. Fox did further testing of PTC with his family and friends (which would obviously not be encouraged today), asking them to describe how the chemical tasted. Interestingly, some found it intensely bitter, some slightly bitter, and some tasted nothing at all.

Following this discovery, PTC has been used to detect genetic variation in tasting abilities world-wide. Further research into the cause of why some people can taste PTC and others can't, has shown that people are much more likely to find PTC tastes bitter if other members of their family do too. Remarkably, the evidence was thought to be so strongly pointing to a genetic inheritance that PTC tasting ability was used as evidence in paternity tests before DNA tests were available.

A few decades later, in 2003, a single gene responsible for sensitivity to PTC was discovered and reported by Kim and colleagues in the Journal of Science.

PTC paper is used to test whether a person is a "taster", "non-taster", or somewhere in between (source: PTC The Genetics of Bitter Taste).

Kim isolated a gene called TAS2R38 on chromosome 7 which showed three variations differing slightly from one another and inherited as a mendelian recessive trait.

This small difference in the gene, and in the protein that it forms, creates a tongue taste receptor that has a different shape. The altered shape modifies the receptors, which then do not respond to PTC, and the person doesn't find the PTC bitter. Different combinations of the gene determine whether someone will find PTC very bitter, slightly bitter or without taste at all.

PTC is an organosulfur thiourea compound containing a phenyl ring and the chemical group N-C=S, which is responsible for its bitter taste. Glucosinolate compounds that occur naturally in cruciferous vegetables (broccoli, brussels sprouts, cabbage, and kale) share this chemical grouping explaining why some of us like these while others dislike them. Brussels sprouts? No, thank you!

RPA Hospital Rare Diseases Committee

Professor Ron Trent, Director, IPM&B

This new committee is co-chaired by Chief Executive Teresa Anderson and Professor John Rasko with broad representation from RPA departments. It reflects the growing international interest in rare diseases, which individually are rare, but together comprise an important group of genetic conditions that impact across patients, their families and the community.

In 2020, the Commonwealth Minister for Health launched the National Strategic Action Plan for Rare Diseases and there is a strong advocacy group for rare diseases via Rare Voices Australia. Sydney was the first Local Health District to take on board this initiative and partner with Rare Voices Australia to consider clinical care and research issues of relevance to rare diseases.

Historically, RPA Hospital has had a link to rare diseases, with its interest in a form of haemophilia linked to the British royal family (Christmas disease that impacted Queen Victoria's son Prince Leopold). The Rare Diseases Committee is now reviewing the range of rare diseases managed through RPA Hospital specialty clinics and research activities which will lead to better support and care for patients and families of the District.

Omics expansion proposal

Professor Ron Trent, Director, IPM&B

The IPM&B's Strategic Advisory Council (SAC) had its second meeting on 8 June. The role of the SAC is still evolving, although it is essentially a high-level think tank looking at what the IPM&B is doing and possible future directions. An example of this was a proposal at the June meeting from Associate Professor David Sullivan (Chemical Pathology at RPA Hospital) that it was time for the IPM&B to expand it's focus to include metabolomics, proteomics and lipidomics in precision medicine.

There is little argument that these "omics" are impacting and will increasingly contribute to future precision medicine activities in terms of models of care and research. However, an important consideration is the effect that diversification will have on current issues around genetics and genomics that remain challenges in a large campus like Sydney Local Health District, where there are rapid developments underway with links NSW Health Pathology, University of Sydney and medical research institutes. This omics proposal is important and will be an ongoing discussion at the SAC to ensure future IPM&B activities remain a win-win for all omics.

Our Stories

Advancing precision medicine using machine learning and AI

Dr Abdul Baten, Genomics Bioinformatician IPM&B

Precision medicine aims to tailor medical treatments to individual patients based on their genetic makeup, lifestyle, and environmental factors. This personalised approach has shown great promise in improving patient outcomes, reducing side effects, and optimising healthcare delivery. The integration of machine learning (ML) and artificial intelligence (AI) has accelerated the progress of precision medicine, enabling researchers and clinicians to analyse vast amounts of data and uncover valuable insights that were previously unattainable through traditional methods. The core strength of ML and AI lies in their ability to process and analyse complex and diverse datasets efficiently. In precision medicine, these technologies can combine genomics, clinical records, lifestyle information, medical imaging, and other omics data to identify patterns and correlations that inform personalised treatment decisions. ML algorithms can sift through large datasets and extract crucial features, empowering healthcare professionals to make data-driven decisions for each patient.

Major opportunities in precision medicine with AI and ML

Enhanced disease diagnosis

AI and ML powered diagnostic tools have the potential to revolutionise disease diagnosis. These tools can analyse medical imaging, biomarkers and clinical data to achieve more accurate and early disease detection, leading to timely interventions and improved prognosis. In conditions such as cancer and neurological disorders, AI-driven diagnostic models have demonstrated remarkable success, enabling early detection and improving the chances of successful treatment.

Personalised treatment plans

Each patient responds uniquely to treatment, and their genetic makeup, lifestyle and environmental factors influence treatment efficacy and potential side effects. AI and ML algorithms can analyse individual patient data to recommend optimal treatment options based on these factors, enabling clinicians to personalise treatments for better outcomes. AI-driven treatment plans can consider a patient's genetic predispositions, response patterns to therapies, and potential adverse reactions, ultimately increasing treatment success rates.

Genomic interpretation

The human genome is incredibly complex, and interpreting genomic data accurately is vital for precision medicine. AI and ML can handle this complexity and analyse complex genomic data to identify actionable genetic variants associated with diseases. By understanding the genetic basis of diseases, AI empowers researchers and clinicians to develop targeted therapies for patients with specific genetic mutations.

Drug discovery and development

Traditional drug discovery and development processes are often costly and time-consuming. AI and ML can accelerate this process significantly by predicting drug-target interactions, identifying potential drug candidates, and simulating drug effects on specific patient populations. By leveraging machine learning algorithms, researchers can streamline the drug discovery pipeline, leading to faster identification and development of targeted therapies for various diseases.

Prognostic predictions

ML models can predict disease progression and patient outcomes by leveraging historical data. These AI-driven prognostic tools can identify high-risk patients who may require more aggressive interventions or personalised treatment plans. Early prognostic predictions can help healthcare providers intervene proactively, leading to improved patient outcomes and a more efficient allocation of healthcare resources.

Challenges in implementing AI and ML in precision medicine

Data quality and interoperability

The success of AI and ML in precision medicine relies heavily on the availability of high-quality data from diverse sources. Integrating data from various healthcare systems and ensuring data interoperability can be challenging. Improving data quality, standardisation, and promoting data sharing among institutions are crucial steps in overcoming this challenge.

Data privacy and security

As precision medicine involves handling sensitive patient data, ensuring data privacy and security is of paramount importance. Healthcare organisations must implement robust security measures to protect patient confidentiality while complying with data protection regulations. Privacy-preserving AI techniques, such as federated learning and differential privacy, can facilitate collaborative research without compromising patient privacy.

Algorithm interpretability

Machine learning algorithms often operate as "black boxes," making it challenging for clinicians and patients to trust and understand the reasoning behind their predictions. The lack of interpretability may hinder the adoption of AI-driven precision medicine tools. Developing explainable AI models that provide transparent decision-making processes will enhance trust and acceptance among healthcare professionals and patients.

Ethical considerations

The ethical use of AI in healthcare presents several challenges. Issues related to patient consent, potential biases in algorithms, and fairness in treatment decisions must be carefully addressed. Ethical guidelines and governance frameworks are essential in ensuring the responsible and equitable implementation of AI in precision medicine.

Limited diversity in datasets

Biased datasets could lead to biased AI models, affecting the generalisability and fairness of precision medicine approaches. Addressing this challenge requires actively encouraging the collection of diverse and representative datasets that encompass various demographics and population groups.

Steps to address some of the challenges

Data standardisation and sharing

Standardising data formats and encouraging data sharing between healthcare institutions can improve data quality and increase the pool of available data for analysis. Collaborative efforts to create centralised repositories of high-quality data can significantly enhance the effectiveness of AI-driven precision medicine.

Privacy-preserving AI

Implementing privacy-preserving AI techniques, such as federated learning and differential privacy, can protect patient data while still enabling collaborative research across multiple institutions. These methods allow data to be analysed without being directly shared, ensuring patient privacy and data security.

Explainable AI

Researchers and developers should focus on building explainable AI models to enhance transparency and trust in AI-driven precision medicine tools. By understanding the logic behind AI predictions, healthcare professionals and patients can make more informed decisions about treatment plans.

Diversity in datasets

Addressing the issue of biased datasets requires a concerted effort to collect data from diverse populations and demographics. Collaborative initiatives and data-sharing agreements that encompass a wide range of patients can ensure that AI models are more representative and fairer in their recommendations.

Conclusion

Machine learning and AI are reshaping the landscape of precision medicine, ushering in a new era of patient-centred healthcare. The potential to harness vast amounts of data, predict disease risks, personalise treatments, and empower patients represents a paradigm shift in medicine.

While challenges such as data quality, interpretability, ethics, and regulation must be addressed, the opportunities for improving patient outcomes and revolutionising healthcare delivery are immense. As the fields of bioinformatics, ML, and AI continue to advance, so too will their impact on precision medicine, ushering in a future where healthcare is truly tailored to the individual.

Our Stories

Pharmacogenomics initiative to utilise long-read sequencing

Dr Branka Powter, Chief Scientist, IPM&B

Short-read sequencing methods, such as whole genome sequencing, whole exome sequencing and targeted panel testing, have been in widespread use in clinical settings for the diagnosis of many genetic diseases. Even though short-read sequencing has advantages, such as being widely available and cost effective, it is less able to capture more complex structural variants, such as large deletions, translocations or inversions, as well as difficulty mapping pseudogenes and long repetitive regions.

The introduction of long-read sequencing in recent years has increased the ability to identify mutations not detectable via conventional methods of sequencing. The benefit of long-read sequencing is that it does not have to use specific gene targeted methodology and therefore can locate novel pathogenic gene regions and overcome the limitations of short-read sequencing.

Long-read DNA sequencing techniques permit the sequencing of much longer DNA fragments in comparison to traditional short-read sequencing techniques, which can be up to 150kbp long, depending on the technique used.

One of the technologies dominating the long-read sequencing space is Oxford Nanopore Technology's nanopore sequencing. Using this technology, a single stranded DNA molecule passes through a nanopore located in an electrically resistant membrane. An ionic current is applied to the pore and changes to the current caused by the nucleotides present at the pore are detected back and recorded, which is then translated into the nucleotide sequence of the DNA strand which passed through the pore.

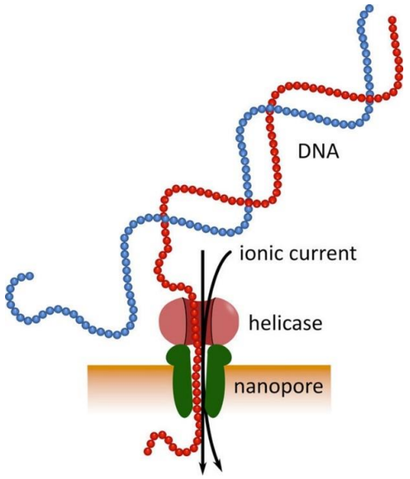


Figure: Schematic representation of long-read sequencing using Nanopore technology (source: Mueller et al., 2019 doi: 10.3791/59377)

The Department of Medical Genomics at RPA Hospital is implementing long-read sequencing for several projects, where there is a need for longer DNA fragments due to the nature of the underlying structural genetic changes. One of the projects is Pharmacogenomics, as the short-read method used to detect single nucleotide variants (SNVs) and copy number variants (CNVs) in CYP2D6 does not correctly phase the duplicated alleles when there is an increased copy number detected.

The CYP2D6 gene locus contains three genes: CYP2D6, CYP2D7 and CYP2D8. CYP2D7 and CYP2D8 are considered CYP2D6 pseudogenes with over 90% of sequence similarity, including several nearly identical regions. This high similarity makes the region highly prone to rearrangements resulting in CYP2D6–CYP2D7 structural rearrangements with hybrid gene structures, which can include different portions of CYP2D6 and CYP2D7 as well as the presence or absence of multiple copies of the CYP2D6 gene. The phasing of such arrangements is difficult using the current short-read methodologies. Long-read sequencing offers promising ability to detect the multiple copies of the not only single gene variants, but also structural arrangements present in the genome. The phasing of CYP2D6 haplotypes, ie, to correctly determine which alleles are duplicated when increased copy number is detected, is important to be able to accurately predict CYP2D6 metaboliser status and to potentially avoid toxicity or reduced efficacy of prescribed medications.

Our Pharmacogenomics team is currently analysing data provided by a team of scientists at the Garvan Institute who utilised Nanopore technology to sequence our samples of interest. We will be able to report on this project again in the near future and hope to implement long-read sequencing to other projects.

Consumer News Update

Dr Alan McPhail, Consumer Representative, IPM&B

A meeting of the Precision Medicine Consumer Group was held on 6 September. This was a follow up from the IPM&B Consumer Engagement Workshop in May and we aim for these ongoing sessions to provide further information about precision medicine plus opportunities for regular health consumer training.

Director, Prof Ron Trent welcomed everyone and outlined IPM&B's commitment to consumer involvement in research. I discussed the role of the consumer and community in research and how their experiences can contribute to the processes of research. Operations Manager, Melissa Cole gave some examples of introductory health consumer training that is available.

Genetic Pathologist Dr Anthony Cheong presented a patient story which illustrated the impact of precision medicine on patient care. It was very interesting to hear how the diagnosis of a genetic condition and targeted treatment resulted in a major improvement in the quality of life for the patient.

A brief update was given on progress by the Consumer Advisory Panel (CAP) of Sydney Health Partners (SHP). The CAP is working on a plan for the components that need to be addressed to ensure that consumers and community are prepared for involvement in research. The components are Governance, Capacity Building, Leadership, Infrastructure and Monitoring. Capacity building includes training, and events; Leadership includes preparing Consumer Champions for the role; and Infrastructure is investigating the necessary attributes and design of a database. The outcomes of this work will be available to all the partners of SHP, including Sydney Local Health District.

After a brief description of the Principles for Consumer Involvement in Research Funded by the Medical Research Future Fund, the meeting closed with a request for consumers to advise the Institute of any topics that they might like covered in future meetings.

Our Stories

Neurogenomics: A focus on the hereditary ataxias

Associate Professor Kishore Kumar, Neurologist and Staff Specialist, Concord Hospital

Advances in technology have facilitated several key recent advances in genomics. These include the discovery and diagnosis of new repeat expansion disorders causing ataxia. These advances are discussed below with a focus on the role that Australian and New Zealand researchers have played in these discoveries.

What is ataxia?

The ataxias are disorders of balance and coordination. They can be autosomal dominant (i.e. spinocerebellar ataxia) or autosomal recessive. Many cases are due to expansions of short repeat sequences (repeat expansion disorders). Up till now, many cases of ataxia have been unsolved.

Recent discoveries have identified the cause of unsolved cases

Recent studies have shed light on the cause of hereditary ataxia, particularly in individuals presenting with late onset ataxia, for both dominant and recessive modes of inheritance. These new genetic forms of ataxia are significant discoveries because they represent some of the most common causes of ataxia to date.

RFC1-CANVAS

Recent advances include the discovery of the cause of Cerebellar Ataxia Neuropathy Areflexia Syndrome (CANVAS) as a biallelic intronic repeat expansion in the RFC1 gene.[1] CANVAS is a disorder that affects many aspects of the nervous system including the cerebellum, vestibular system and peripheral nerves. Initially, a particular motif was identified as pathogenic – AAGGG. Subsequently, different motifs were found to be pathogenic. An example of this is an (AAAGG)10-25(AAGGG) expansion in New Zealand Māori and Cook Island Māori individuals, identified by Australasian researchers.[2]

Furthermore, we contributed to a recent study which found that the expansion of the AAAGG motif,[3] a motif that was originally thought to be normal,[4] can be pathogenic for CANVAS. Additionally, we (with Prof Marina Kennerson) have found that the RFC1 expansion could mimic Sjorgen's syndrome and hereditary sensory neuropathy with cough.[5] Finally, it is now apparent that truncating variants in the RFC1 gene can also cause CANVAS.[6] This points to a potential loss of function mechanism, although we need to learn much more about the disease mechanisms underlying RFC1-CANVAS.

GAA-FGF14 (SCA27B)

A further major discovery is that GAA expansions in the FGF14 gene are a common cause of late onset autosomal dominant ataxia. This discovery was made by Prof Paul Lockhart in Melbourne[7] and a team in Canada, with Australian collaborators.[8] This could explain about 10% of unsolved cases of ataxia but higher in certain ethnic groups like French-Canadians. This form of ataxia may respond to a certain treatment – 4 amino-pyridine.

Nanopore sequencing can change the diagnostic paradigm for the ataxias

In a landmark study with Dr Ira Deveson (Garvan Institute), we showed that targeted Nanopore sequencing was an accurate approach to detecting a range of repeat expansions.[9] We have subsequently used this approach to diagnose additional cases with a range of neurological disorders.[10, 11] This could replace outdated, existing approaches, and has the potential to be more comprehensive, rapid and cheaper (see Figure). We are working with Dr Anthony Cheong, Genetic Pathologist at the Molecular Medicine Laboratory, to develop this test for clinical practice.

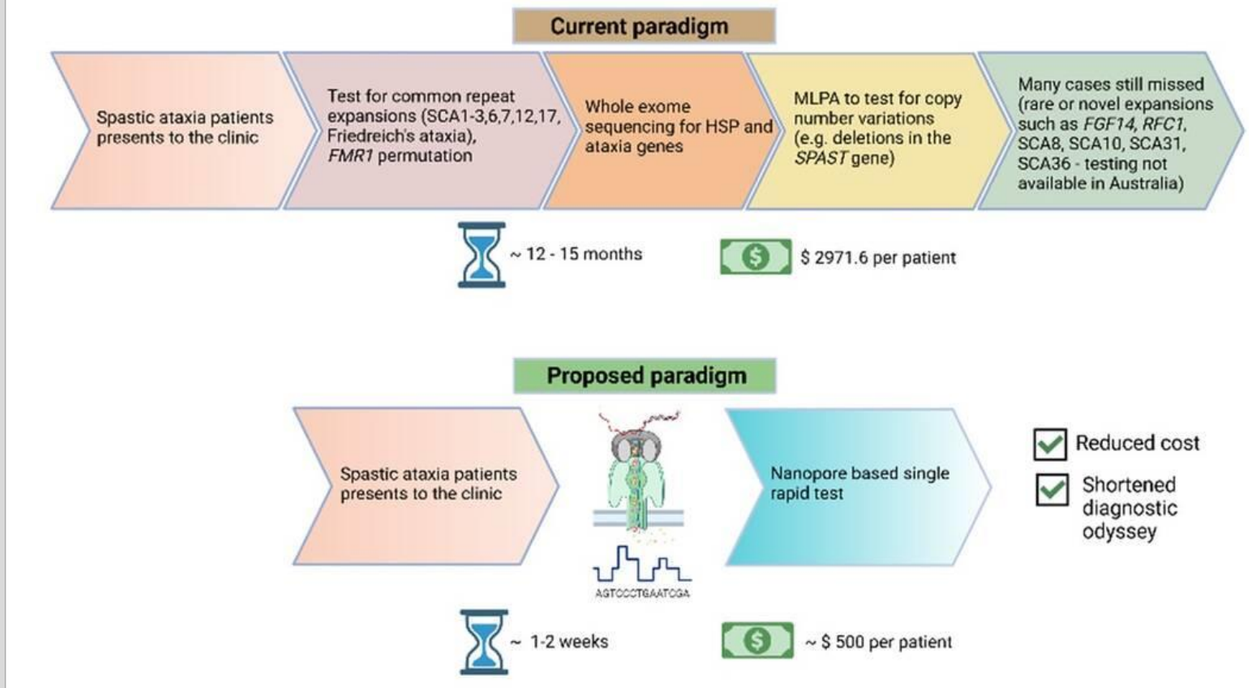


Figure. A streamlined approach using Nanopore has several potential advantages over the existing diagnostic approach for patients with disorders of spasticity &/or ataxia. Acknowledgements, Drs Ramesh Narayanan and Laura Rudaks for assistance with the figure.

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Our Stories

Cloud computing: Bioinformatics and Genomics

Current trends and future prospects

Dr Abdul Baten, Genomics Bioinformatician
IPM&B

In the ever-evolving landscape of biomedical research and healthcare, the integration of cloud computing has emerged as a transformative force, particularly in the realms of bioinformatics and genomic analysis. Bioinformatics, the intersection of biology and data science, in particular, has witnessed a paradigm shift. Traditionally, High-Performance Computing (HPC) and local storage systems were the backbone of bioinformatics research. However, the rise of cloud-based bioinformatics has transformed the landscape, offering unprecedented scalability, accessibility, and collaboration. In this article, we will explore this transition from traditional HPC and storage to cloud-based solutions, and discuss advantages, pitfalls, essential considerations, and future trends in this dynamic field.

Advantages of cloud-based solutions

Traditionally, bioinformatics researchers encountered limitations such as restricted scalability, high infrastructure costs, and limited accessibility. They often grappled with fixed computing resources and long queue times on shared systems. The explosion of genomic data has made it challenging to manage and store vast datasets locally. Local storage solutions often lacked the flexibility to accommodate the dynamic and growing nature of genomic data. In contrast, cloud platforms provide secure and reliable data storage, ensuring accessibility from anywhere in the world, fostering global collaboration, and eliminating geographical barriers. Moreover, cloud-based solutions facilitate real-time access to data, enabling researchers to make informed decisions swiftly.

This is particularly crucial in an emergency situation in a healthcare setting, where rapid analysis of genetic, genomic or other related data can guide treatment options and improve patient outcomes. Cloud-based storage solutions also provide efficient data management, with features like automatic backups, versioning, and robust security protocols.

In addition to real-time access, cloud platforms offer a dynamic environment where computational resources can be scaled up or down based on the specific needs of the project. This scalability ensures that researchers have the computing power required for tasks ranging from routine data analyses to large-scale genomic studies. Services like Amazon Web Services (AWS), Google Cloud Platform (GCP), and Microsoft Azure provide vast computing power and storage capabilities, enabling seamless collaboration and efficient data management. They have also introduced a paradigm shift in cost management for projects requiring bioinformatics or statistical analysis of the data. Researchers can avoid the upfront capital costs associated with building and maintaining on-premises computational infrastructure. Instead, they pay for the resources they use, optimising budget allocation and fostering cost-effective research.

Pitfalls and challenges

While cloud computing and storage offer numerous advantages, they also come with certain limitations and challenges. Data security and privacy are critical concerns, especially when dealing with sensitive genomic information. Robust security measures and compliance with regulatory standards are essential to ensure data security and privacy. Meeting regulatory requirements and industry-specific compliance standards can be challenging in a cloud environment, especially when data is stored across multiple geographical locations. The physical location of data stored in the cloud can raise concerns about data sovereignty and compliance with local regulations. Some users may be hesitant to store data in locations with different legal frameworks.

Cloud service providers may experience downtime due to various reasons such as maintenance, hardware failures, or cyber-attacks. This can disrupt services and impact institutions that rely heavily on cloud resources. Access to cloud services is contingent on a reliable internet connection; if there are connectivity issues, users may experience disruptions in accessing their data and applications.

While cloud services offer scalability, costs can become unpredictable, especially if usage patterns fluctuate. It is crucial for users to carefully manage and monitor their resources to avoid unexpected expenses.

The transition to cloud-based solutions may require researchers to acquire new skills and adapt to different workflows. Training and support are crucial for a smooth transition.

Future outlook

Cloud computing provides the infrastructure for storage, computation, and data analysis in a centralised manner. Edge computing complements this by extending the capabilities to the edge of the network, allowing for local processing and reducing the need to send all data to the cloud. Edge computing achieves near-instantaneous data processing and storage by positioning computing systems in close proximity to the devices, applications, or components responsible for data collection or generation. The integration of edge computing in healthcare is anticipated to grow, especially in cases requiring real-time analysis of patient data, enabling quicker decision-making.

Cloud computing will play a pivotal role in advancing genomic medicine. The integration of genomic data with clinical information, facilitated by cloud platforms, will lead to more personalised and targeted treatments, potentially revolutionising disease diagnosis, prognosis, and treatment strategies.

Serverless computing, also known as Function as a Service (FaaS), is a cloud computing model where cloud providers automatically manage the infrastructure needed to execute and scale applications.

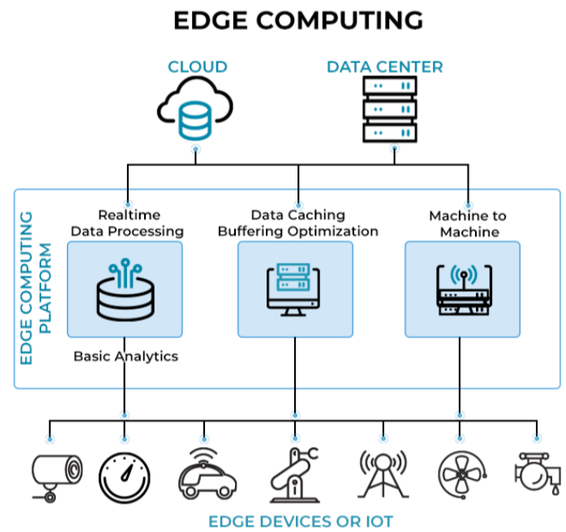

Figure. Edge computing (source: Spiceworks)

In a serverless architecture, developers write and deploy individual functions or pieces of code, and the cloud provider takes care of the execution environment, scaling, and maintenance. The adoption of serverless computing models will simplify resource management, allowing researchers to focus on analysis rather than infrastructure management.

In conclusion, the transition from traditional HPC and storage to cloud-based solutions signifies a revolutionary shift in bioinformatics and genomics research and applications. While presenting numerous advantages in scalability, accessibility, and cost-efficiency, researchers must navigate potential pitfalls and consider critical factors such as data security, compliance, and collaboration. The future promises even more innovations, with advanced analytics, serverless computing etc., poised to further elevate the capabilities of cloud-based bioinformatics and genomic solutions. As the field continues to evolve, embracing these technological advancements will be key to unlocking new frontiers in genomics and personalised medicine.

Our Stories

Sydney Biomedical Accelerator

Precision Medicine Research Facility

Professor Ron Trent, Director, IPM&B

Activity around designing the Sydney Biomedical Accelerator (SBA) continues with many involved to ensure it will be a state-of-art research precinct with Sydney Local Health District and the University of Sydney working side by side and collaborating across multiple disciplines.

A few weeks ago, the District's Internal Advisory Committee recommended that the last remaining space in the SBA would be a purpose-built Precision Medicine Research Facility (PMRF) to enable new discoveries expected in precision cancer to be accelerated from research to clinical practice, and new technologies (presently the focus is third generation long read sequencing) to be applied more rapidly into clinical practice.

The PMRF, occupying about 280m2 of laboratory space, will act as a conduit between the innovative clinical care using precision medicine practised at RPA Hospital and the genomic testing conducted under NSW Health Pathology at RPA Hospital. Departments/laboratories that will benefit are those particularly involved in cancer genomic testing (Medical Genomics, Tissue Pathology & Diagnostic Oncology, Neuropathology and Molecular Haematology).

The proposed PMRF is located on level 1 of the SBA's building B next to Gloucester House (SBA building A). The position will ensure rapid access to bioinformatics resources that are being developed within Gloucester House and access to the many sophisticated technologies across the entire SBA complex.

A big thank you to Associate Prof Bing Yu, who is providing expert advice on what the PMRF might look like, and how to design it to NATA accreditation standards, ensuring no delay when discoveries in the PMRF are moved to the clinical testing laboratories at RPA Hospital. From Sydney Local Health District, Penny Schmidt and Associate Professor Vicki Taylor have been very supportive of this initiative. Hopefully, some draft plans will soon be available to show members of the IPM&B, and then ideas on what to start on will follow even though the building is not yet there!

Genetic Counsellor Awareness Day

Genetic Counsellor Awareness Day was celebrated on 9 November to raise awareness and interest about the profession and the valuable role genetic counsellors play in health care. Genetic Counsellors and Clinical Geneticists from across Sydney Local Health District came together for a morning tea and photoshoot to promote genetic counselling services across the District.

Genetic counsellors are trained to explain family history information and genetic test results to help people make informed decisions about their health. Genetic counsellors work directly with patients across the District, in areas including cancer, pregnancy, cardiology, neurology, infertility, paediatric and adult medicine. Many others do research or work in education, public health, academia, laboratories, or industry settings.

Kathleen Le Marquand, Laura Molloy and Shona Reid of the Clinical Genetics Service also travelled to Canberra for a Genetic Counsellor Awareness Day event arranged by the Australasian Society of Genetic Counsellors and Human Genetic Society of Australasia. Three Senators, Dr Mike Freelander, Dr Monique Ryan and Wendy Askew, who are considered Parliamentary Friends of Rare Diseases, attended and spoke about their respect and support of genetic counsellors in the healthcare workforce.

The meeting was aimed at promoting the vital role of genetic counsellors in the future of precision medicine. "I am proud to belong to a dedicated team of genetic counsellors in the District, and Genetic Counsellor Awareness Day is the perfect time to celebrate our important group as allied health professionals and to promote our services," said Kathleen Le Marquard, Senior Genetic Counsellor, IPM&B.

MRFF Research Grant

Investigating the genetic causes of Parkinson's disease

Associate Professor Kishore Kumar and team at the Garvan Institute of Medical Research have been awarded a grant from the Medical Research Future Fund Genomics Health Futures Mission to investigate genetic causes of Parkinson's disease.

The research project aims to improve the genetic diagnosis of monogenic Parkinson's disease and identify disease-causing variants in known and previously unknown genes. Associate Professor Kumar's team will employ advanced genetic testing techniques and cutting-edge data analysis tools to analyse DNA samples from 1,000 Parkinson's patients, making it one of the largest registries of Parkinson's worldwide.

Our Stories

The Human Pangenome

An exciting new era for human genomics and genetic diagnostics

Professor Marina Kennerson, Deputy Director, IPM&B

The release of the draft human pangenome in May this year[1] is set to change the genome reference landscape as we unravel the genetic diversity of humans and use this information in the realm of disease gene discovery and future genetic diagnostics.

What is the human pangenome?

The human pangenome is a comprehensive representation of the entire spectrum of genetic variation in the human population. The traditional reference genome used for the last 20 years and referred to as GRCh38 or more recently the “gapless assembly” T2T-CHM13 reference[2], is based on non-phased linear sequence mostly coming from a single individual. In contrast, the draft human pangenome reference is the genetic sequence data from a diverse range of human genomes (47 index children from sequenced trios) that have been integrated, compared, and annotated to generate the combined sequences for 94 phased haplotypes (Figure 1A).

Key to completing the pangenome reference is the sampling of genomes that will undergo sequencing. Achieving the pangenome diversity will rely on ensuring that the principles of diversity, equity and inclusion are used to select the remaining individuals for sequencing and generating 700 phased haplotypes by the end of 2024. It is envisaged that the pangenome will capture the DNA variants common to all individuals as the “core genome”, and the 0.4% average difference between individuals as the “accessory genome” in which unique variants specific to an individual (cloud genome) or population and ethnic group (shell genome) are represented (Figure 1B).

How will we view the human pangenome?

To collectively summarise all variations in every individual in a single structure, graph representation of the pangenome reference will provide a more accurate and versatile model for understanding human genetic diversity. Instead of the linear, one-dimensional structure of a traditional reference genome, the graph will include multiple branching paths and connections to represent the different alleles and variants found in the human population (Figure 1C). Importantly, graphing the pangenome reference will be a dynamic framework that can adapt and expand as new genetic material is generated, making it an invaluable resource for genomics research and personalised medicine.

The pangenome and structural variation

Structural variation (SV) is a class of variant representing large genomic rearrangements (>50 bp to millions of bp) including duplications, deletions, inversions, insertions, translocations and repeat expansions. We are utilising the human pangenome reference to discover structural variation mutations in families with Charcot-Marie-Tooth (CMT) neuropathy, the most common inherited peripheral nerve disease presenting in neuromuscular clinics. Our team has recognised SV as an important lens to solve CMT families[3-5]. For our remaining unsolved CMT families excluded for genome wide coding mutations, we are working with Dr Georgie Samaha (Sydney Informatics Hub, University of Sydney) to compare patient short read WGS (srWGS) to the draft pangenome reference. As a comparative reference map for srWGS, the draft pangenome has added 119 Mb of new DNA, increased accuracy of SNV and indel discovery by 34% and increased the detection of SV by 104%. The comparative power of the pangenome reference for SV discovery will eliminate the biased “street lamp effect” of the hg38 reference and is facilitating interrogation of our unsolved CMT families for the next lowest hanging fruit in the difficult non-coding “dark” genome.

An exciting future for comprehensive diagnostic genetics

The use of the pangenome reference in the wider research genomics community is in its infancy and will take time to implement in a clinical diagnostic setting. However, as tools develop to make clinical utility of the pangenome reference easier, this will provide a comprehensive and personalised view of an individual's genetic makeup. This depth of genetic information will enhance the accuracy of genetic testing, enabling more precise disease risk assessment, personalised treatment recommendations, and pharmacogenomic insights. The pangenome's potential to uncover new genes and variations offers an exciting avenue for advancing research and diagnostics by unlocking a wealth of genetic insights that will hold the key to more tailored and effective healthcare and an era of truly personalised medicine.

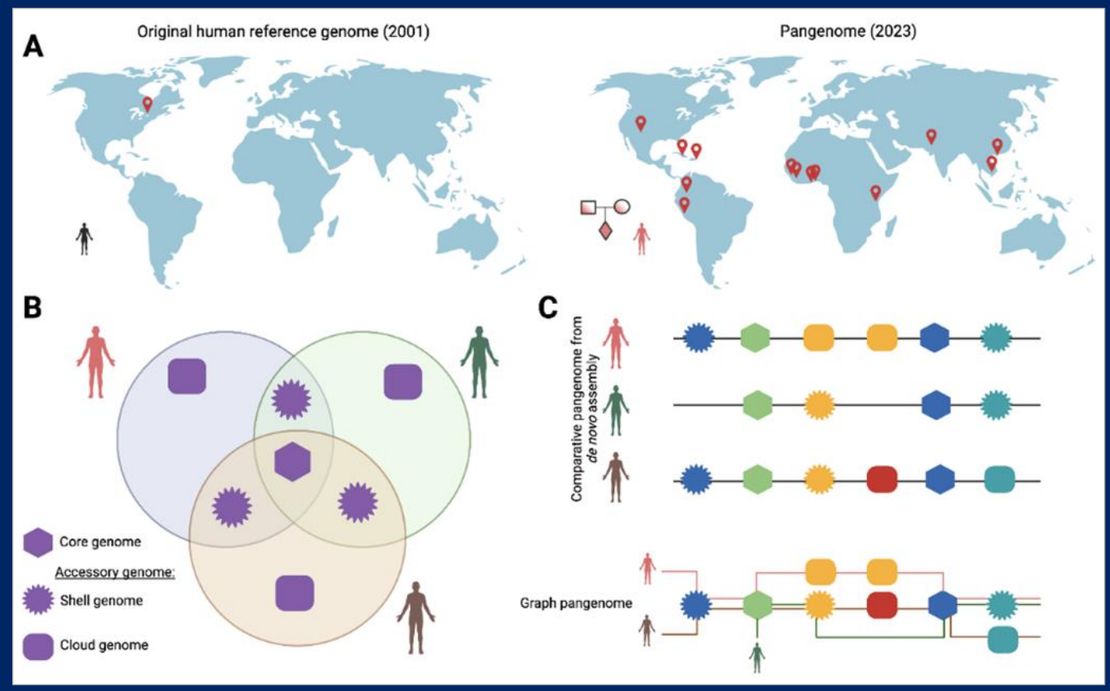

Figure 1. (A) The original reference genome is based on sequence from a single individual whereas the complete pangenome reference will be the collective sequence of genomes from 350 individuals selected by diversity, equity and inclusion.

(B) The pangenome reference will consist of the core and accessory genome to collectively represent variation from all sequenced genomes.

(C) Comparative and graph interpretation of the pangenome based on 3 sequenced individuals. The colours represent elements in the same position. The pangenome reference will be linear for common sequence (hexagon). The branching shows the variation between the individuals for the designated position of the variant. The pink individual has a duplication of the third element which is different to other individuals, making the duplicated element part of the cloud genome.

Panels B and C have been adapted from Abondio et. al. 2023[6]. Acknowledgements, Dr Ramesh Narayanan for assistance with the figure.

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Connect with us

Institute of Precision Medicine &
Bioinformatics
Sydney Local Health District
Royal Prince Alfred Hospital
Building 65, Level 6 Missenden Rd
Camperdown NSW 2050

Phone (02) 9515 5300
Email SLHD-IPM&B@health.nsw.gov.au

Web
slhd.health.nsw.gov.au/ipmb

LinkedIn
linkedin.com/company/institute-of-
precision-medicine-bioinformatics

X
@SLHD_IPMB