Sydney Local Health District

Institute of Precision Medicine & Bioinformatics

ANNUAL REPORT 2024

Published: March 2025

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 2024 is a review of our achievements and highlights over the last year and includes information about our activities and performance.

Acknowledgements

I am grateful to the many health professionals who assisted the IPM&B during 2024.

Dr Teresa Anderson AM, a dedicated advocate for precision medicine, is now leading the implementation of the Single Digital Patient Record, an initiative set to transform the patient journey across all NSW Health care facilities. Teresa leads by example and has played a key role in many of the success stories emerging in precision medicine at the District.

David Norwood and the District's Digital Health & Innovation team for their patience and enthusiasm when we met obstacles trying to move large datasets across the digital network.

Associate Professor Bing Yu and his talented laboratory scientists in precision cancer, who are always looking for new genomic and transcriptomic tests to improve patient care.

Dr Abdul Baten for strengthening our collaboration with digital health and bioinformatics at USYD, a partnership we hope will continue to grow.

Dr Anthony Cheong and the Molecular Medicine laboratory team at Concord for their impressive performance with neurogenetics genome testing.

Dr Alan McPhail, who continues to contribute to the IPM&B by advocating for the inclusion of consumer views in all aspects of precision medicine models of care.

Melissa Cole, who has been the Operations Manager since the launch of the IPM&B in 2020. Melissa has produced the IPM&B Annual Report each year, but this will be her final one as she transitions to a role outside of NSW Health in 2025. We will miss you, Melissa.

Professor Ron Trent
Director, Institute of Precision Medicine & Bioinformatics

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Front cover:
Dr Zoe Marks, Medical Trainee
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RPA Hospital

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Acknowledgement of Country

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

Our District acknowledges *Gadigal*, *Wangal* and *Bediagal* as the three clans within the boundaries of 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

2024 was a year of transition, marked by a post-COVID-19 budget deficit and leadership changes at Sydney Local Health District. Teresa Anderson AM stepped down as our Chief Executive to take on the leadership of the NSW Health Single Digit Patient Record (SDPR) rollout. Teresa was a strong advocate for numerous innovative clinical initiatives across the District. We welcome Deb Willcox AM as our new Chief Executive. Deb has deep ties to the District and a proven track record in healthcare, positioning us well to navigate key changes in precision medicine at both RPA and Concord hospitals, as well as the Sydney Biomedical Accelerator (SBA), a collaboration with the University of Sydney. USYD also faced challenges in 2024, and towards the end of the year, Professor Robyn Ward AM, Executive Dean for Medicine and Health Sciences and a key figure in the SBA initiative, left to take on a senior academic role at Monash University.

A highlight in 2024 was the measured launch by the Department of Medical Genomics at RPA Hospital of a pharmacogenomics (PGx) initiative. PGx has long been described as a key component of precision medicine since it moves the spotlight further into preventive proactive medicine rather than the traditional reactive responses to drug side effects. PGx is particularly relevant in current times with a clinical environment of polypharmacy due to the aging population, and an emerging but growing list of biological therapies.

After extensive consultation across the District, it was determined that a comprehensive 20-gene panel using modern genomic analysis platforms was not the preferred option for PGx testing. Instead, a more targeted, disease-specific panel approach was adopted.

Another significant event in 2024 was the confirmation that while cloud computing offers numerous benefits, it also presents considerable challenges, particularly in terms of privacy and cybersecurity. Nevertheless, cloud computing is the only option going forward to deal with large data sets, as the NSW Health Ministry has mandated a move from locally maintained mainframe computer facilities to more universally accessible cloud computing. This change required a re-think by the IPM&B and a stronger alignment with the District's Digital Health & Innovation (DH&I) facility which will be described in more detail below. The flexibility available with cloud computing also highlighted the short and long-term benefits of artificial intelligence (AI) in clinical and laboratory medicine. The focus on AI reminded me of a comment made by a staff member a few years ago that genomics did not need a bioinformatician when this position was being proposed as a new initiative for the IPM&B.

The reason given was that emerging AI would make a genomics bioinformatician redundant. However, reality now shows without bioinformatics expertise, the benefits of AI are not achievable since a growing list of regulatory and governance requirements must be implemented to ensure the safe use of AI in clinical applications. In particular, is an understanding by the users of how the AI "black box" works.

A highlight in 2024 was the IPM&B's Precision Medicine Consumer Group ably led by Dr Alan McPhail. Although relatively small, the group brings to the IPM&B important ideas to ensure the Institute never loses sight of its core goal, which is to focus on the needs of patients and families across the District and beyond.

I would like to acknowledge the work of many who helped to move the IPM&B forwards during a demanding 2024. The restructured IPM&B Strategic Advisory Council continues to contribute through out-of-the-box thinking, providing many ideas for discussion, and a regular reminder for the IPM&B to review the purposes for its formation.

I spent many productive hours with the generous Pam Garrett, Head of Planning at Sydney Local Health District, discussing the future direction of precision medicine from 2024 to 2029.

More will be said on this in the Annual Report under the District's Healthcare Services plan.

Professors Clement Loy and Marina Kennerson, the IPM&B's Deputy Directors were always available to answer my questions and comment on ideas or initiatives.

David Norwood and his team in DH&I helped resolve complex network challenges that would otherwise have negatively impacted the ongoing work of the somatic and haematological cancer teams.

I am grateful that the enthusiastic collaborator, Professor Tim Lambert, has taken on the challenging task of incorporating PGx into the model of care for patients with mental health disorders. His insight has been invaluable for those working in the laboratory.

Dr Alan McPhail and the Precision Medicine Consumer Group contributed to planning for PGx and other topics.

Melissa Cole, the Operations Manager, was always quick to respond to the numerous requests from members of the IPM&B. Her efforts in setting up and maintaining the IPM&B website are greatly appreciated.

Director
Professor Ron Trent

2024 Activity

Somatic Cancer Testing Service

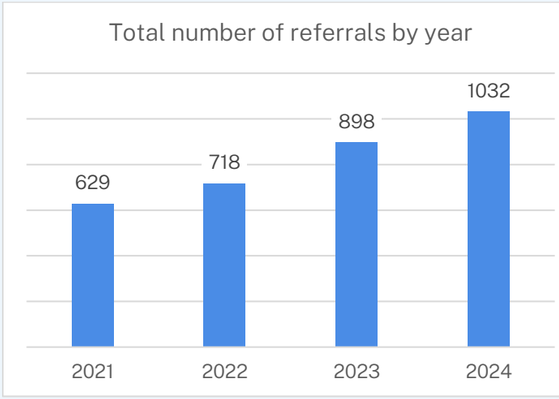
Highlights

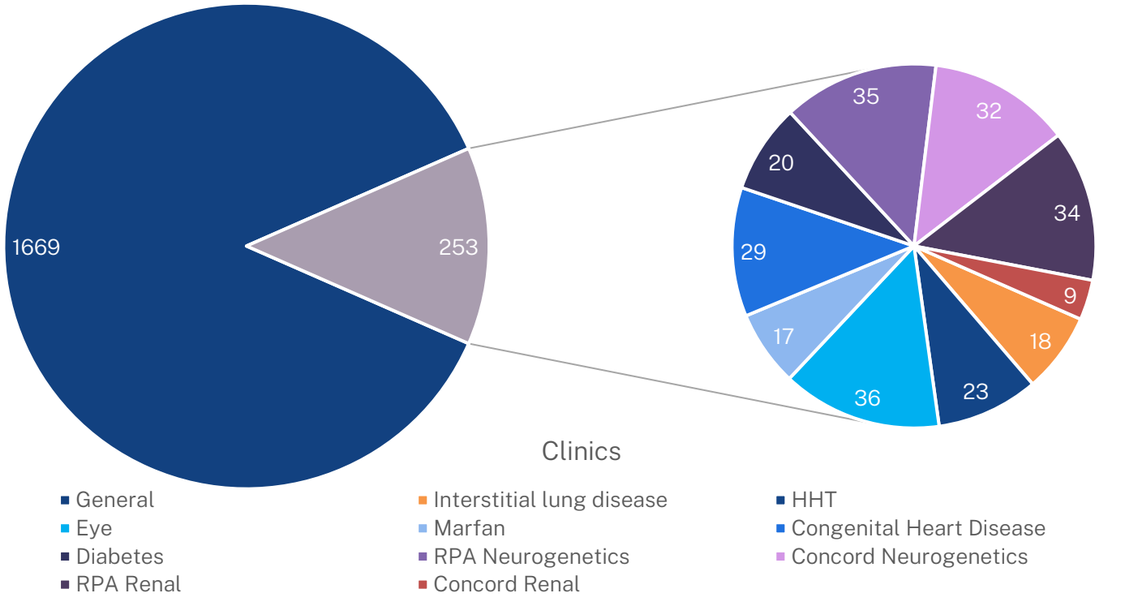
In 2024, the Somatic Cancer Testing Service made notable advancements in cancer diagnostics, primarily through the integration of advanced sequencing platforms and the expansion of testing capabilities. The successful integration of Illumina MiSeq and NextSeq platforms into a secure network enabled seamless remote analysis, meeting both functional and security requirements for Sydney Local Health District and NSW Health Pathology. Additionally, the laboratory expanded its capabilities by incorporating the Thermo Fisher Genexus platform, which increased cancer-related gene targets and introduced liquid biopsy testing for both cfDNA and cfRNA. These efforts facilitated the detection of additional actionable gene fusions in non-small cell lung cancer, enhancing the laboratory's ability to support personalised treatment strategies.

The laboratory also made significant progress in refining its testing protocols and exploring new technologies to improve cancer diagnostics. Key achievements included the development of highly sensitive droplet digital PCR assays for detecting driver mutations and resistance mutations, which allowed for real-time monitoring of tumor burden and treatment responses. Furthermore, continuous quality improvements in next-generation sequencing testing protocols resulted in a reduction of sequencing failure rates to 0%, optimising the accuracy and reliability of results. With the addition of trained staff and ongoing support for research and development, the Somatic Cancer Testing Service has strengthened its capacity to provide cutting-edge diagnostic services, ensuring more accurate and timely cancer care for patients.

Clinical Genetics Service

Highlights





IPM&B Engagement and education

Highlights

316 attendees to IPM&B webinars	76 attendees to IPM&B events	820 views IPM&B e-News	1,584 views IPM&B website	37% increase LinkedIn followers	11% increase X followers

Services

Precision Cancer

Milestones in somatic cancer testing 2024: facilitating precision treatment

Associate Professor Bing Yu
Head, Somatic Cancer Testing Service

Somatic cancer testing is an integral part of precision oncology, bridging the gap between molecular diagnostics and individualised patient care. By identifying actionable targets, overcoming challenges in variant interpretation, and leveraging innovative technologies like liquid biopsy, this approach continues to transform the landscape of cancer treatment. The laboratory staff in the Somatic Cancer Testing Service achieved remarkable milestones in 2024.

Secure network integration of Illumina platforms

After extensive testing and validation, all the Illumina MiSeq and NextSeq platforms were securely integrated into an isolated network. This not only fulfilled the sequencing company's requirements for instrument functionality but also met the security and safety needs of the District's network. The output data can pass to the NSW Health Pathology cloud host, enabling remote analysis. This initiative was coordinated by Cassandra Bruce (IPM&B Senior Hospital Scientist) and Dr Hugh French (genetic pathology registrar), with support from Illumina and ICT teams at the District and NSW Health Pathology.

Expansion to Thermo Fisher Genexus platform

The laboratory expanded next generation sequencing (NGS) testing capabilities from Illumina platform to the Thermo Fisher Genexus system. The development and validation of the Genexus Oncomine Precision Assay (OPA) were led by Jie Qian (IPM&B Hospital Scientist). Accreditation of Genexus OPA increased the number of cancer-related target genes from 20 to 50 and expanded liquid biopsy testing from cell-free DNA (cfDNA) to cell-free nucleic acid (both cfDNA and cfRNA).

Additionally, the OPA facilitates gene fusion detection from formalin fixed paraffin embedded (FFPE) RNA, which can identify additional 16% actionable fusions in non-small cell lung cancer (NSCLC) beyond the routine DNA test (for example, 20-25% discovery rate of EGFR mutations in NSCLC). Consequently, the implementation of Genexus OPA can maximise driver mutation detection and assist with determining effective treatment strategy. A separate method for gene partner agnostic fusion detection was also established and accredited under the leadership of Cassandra. These achievements meet the Medicare testing requirements for access to new and emerging targeted drugs, such as entrectinib, larotrectinib, selpercatinib and tepotinib, while delivering faster profiling results to requesting doctors.

Curation and interpretation of variants

Variant curation and interpretation remain a significant challenge in somatic cancer as the volume of NGS data grows. With the invitation from the NSW Health Pathology Statewide Sequencing Service, the laboratory joined Omico's PrOSPeCT project in May 2024 and contributed to TSO 500 comprehensive genome profiling in curation and reporting. This work was delivered by Cassandra Bruce and Spiridoula Kraitsek (NSW Health Pathology Scientist).

The team also participated in the weekly multidisciplinary team meetings and discussed difficult or unusual cases, ensuring comprehensive variant interpretation.

Advancements in liquid biopsy using ddPCR

Liquid biopsy, or cfDNA testing, has revolutionised cancer management with its minimally invasive approach and real-time monitoring capabilities. The laboratory initiated cfDNA monitoring using droplet digital PCR (ddPCR), a highly sensitive and specific technology. This development was spearheaded by IPM&B scientist, Dan Chen.

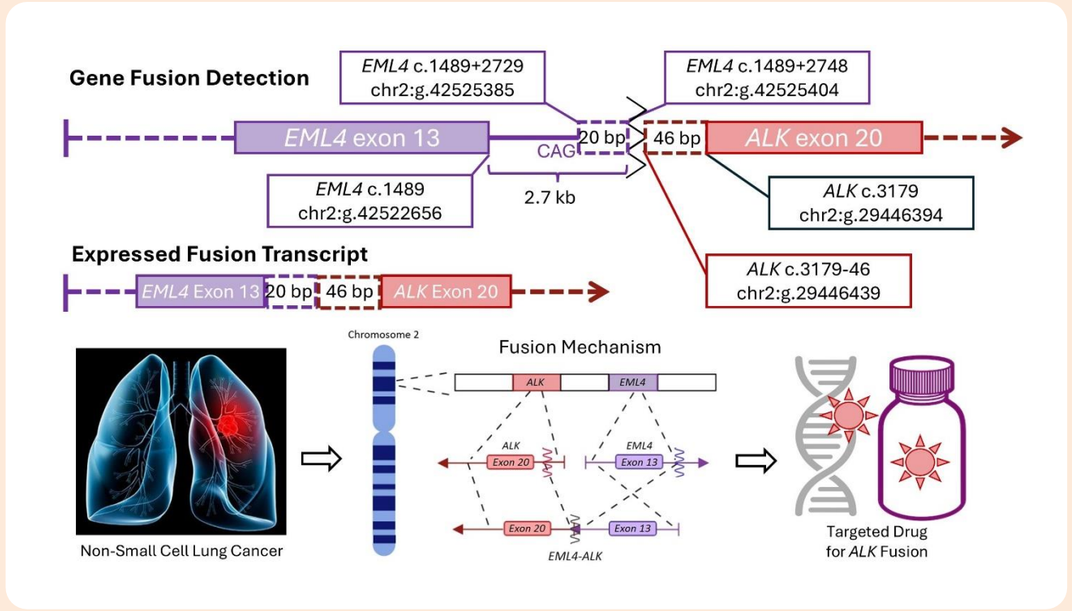


Figure. Gene fusion detection using Genexus OPA and enabling targeted treatment.

The team successfully developed and validated ddPCR assays for key driver mutations, which so far include EGFR L858R, KRAS G12C, BRAF V600E and RNA-based MET exon 14 skipping. These assays allow dynamic assessment of tumour burden, treatment response, molecular residual disease, and progression or relapse.

Additionally, the laboratory established ddPCR assays for detection of resistance mutations including EGFR T790M (resistance to first-generation tyrosine kinase inhibitors) and EGFR C797S variants (resistance to third-generation osimertinib).

Improvement of NGS testing service

Continuous quality improvement is a core goal for diagnostic laboratories. After 18 months of NGS testing using Archer VariantPlex Solid Tumor Focus panel (v1), the laboratory reviewed sequencing data from 1,070 cases across 56 runs. This analysis, led by Dan, revealed a 1.3% (20/1550) failure rate due to poor-quality FFPE samples, which interfered with the sequencing coverage of other samples in the same run.

Based on these findings, the laboratory updated the NGS protocol, incorporating stricter input criteria for FFPE DNA, enhanced library quantification and refined sequencing loading calculations. These updates reduced the failure rate to 0% over 220 subsequent sequencing cases.

New staff training and routine service delivery

Three new staff members were systemically trained. These new staff contribute to the wet laboratory work of the routine cancer NGS testing. This significantly supported the research and development work carried out by other scientists.

Somatic cancer testing has become a cornerstone of precision oncology, offering transformative benefits for managing patients with solid tumours. By tailoring treatment strategies to the molecular profile of an individual's tumour, somatic testing not only enhances survival outcomes but also significantly improves the quality of life for cancer patients. This rapidly advancing field integrates novel approaches to diagnosis, treatment selection, and prognosis, underscoring its importance in contemporary cancer care.

Clinical Genetics

Dr Lisa Worgan
Head, Clinical Genetics Service

The Clinical Genetics Service at Sydney Local Health District continued to provide inpatient and outpatient consultations for adult, paediatric, neonatal and prenatal patients. The service provides genetic assessment, genetic counselling and facilitates genetic and genomic testing for a wide range of patients. The clinical genetics service continued its involvement in general genetics clinics, prenatal clinics as well as subspeciality clinics at both RPA and Concord Hospitals. Many of the subspecialty clinics are multidisciplinary clinics that provide integrated and timely genetic assessment in collaboration with other specialties. These clinics include Neurogenetics Clinics at RPA and Concord, Renal Genetics, Interstitial Lung Diseases Clinic, Hereditary Haemorrhagic Telangiectasia Clinic, Genetic Eye Diseases Clinic, Young Adult Diabetes Genetic Clinic, Marfan and Aortopathy Clinic, Congenital Heart Diseases Clinic and Immunogenetics. As mainstreaming of genetic testing has advanced this year, the Clinical Genetics Service also provides support to non-genetic specialists in arranging genetic testing by providing counsellor support for obtaining consent, advice on appropriate testing and assistance with interpretation of results.

In 2024, the Clinical Genetics Service consisted of four Clinical Geneticists (2.5FTE) including Dr Lisa Worgan, Dr Felicity Collins, Dr Amali Mallawaarachchi and Dr Alison McLean. Dr Noe Nunez Martinez also worked with the team in a locum position and will continue in this role in 2025. The genetic counselling team included 3.0FTE positions in general genetics and 1.0FTE position in Hyperlipidaemia and Porphyria Service. Kathleen Le Marquand serves as the clinical supervisor for the team of genetic counsellors at IPM&B, which includes Laura Molloy, Shona Reid, Ella West, Rachel Xifaras, and Madeline Calder. Together, Kathleen, Laura, Ella, Rachel, and Madeline actively promote genetic counselling services across the District, collaborating with various clinical specialties.

The Clinical Genetics service was supported by 2.8FTE administrative officers; Rose O'Donoghue, Julie Fua and Rayaca Tayabally filled these roles in 2024.

In 2024, we welcomed our first advanced trainee in Clinical Genetics, Dr. Rachel Bowden, who completed a year of advanced training in Clinical Genetics at RPA Hospital. The addition of an advanced trainee to the team offered valuable training opportunities and made a significant contribution to teaching, academic, and clinical services, resulting in a notable reduction in wait times for outpatient appointments. Unfortunately, this position has not been funded for 2025, but we will continue to advocate for this position in the coming year. Education provided by the Clinical Genetics Service includes personalised medical student placements, developing medical student MD projects, delivering BPT teaching, presenting at grand rounds, serving as medical student learning advisors, and overseeing genetic counselling student placements.

Team involvement in committee, advocacy, and research roles

Many team members actively participated in committee work, advocacy, and research throughout 2024. Dr Worgan continued as the co-chair of the Clinical Genetics Network Executive Committee at the NSW Health Agency for Clinical Innovation and was on the steering committee for the NSW Health Genomics Steering Committee. Drs Collins and McLean both continued roles with the Human Genetics Society of Australasia (HGSA). Dr Collins completed a preliminary scoping study of genomic unmet needs in Australia. Dr McLean was on the Education, Ethics and Social Issues Committee within the HGSA. She is also involved in research projects including the IMPEDE-PKD study at RPA Hospital, the ALIGNED Study through St Vincents and Amyloidosis research through Westmead Hospital. Dr Noe Nunez Martinez is currently on the organising committee for the HGSA conference in 2025 and is involved in research projects including genomic screening for newborns.

Pictured: NSW Genetic Counsellors coming together for a day of connection and learning at Genetic Counsellor Awareness Day.

Dr Amali Mallawaarachchi continues her research in genetic renal disease and was co-chair of the National KidGen Kidney Genetics MDT and also part of the Clinical Academic group in Genomics and Precision Medicine Partnerships funded through Sydney Health Partners.

Genetic counselling

Kathleen Le Marquand is the Senior Genetic Counsellor for Sydney Local Health District and serves as the lead for the genetic counsellors' allied health group, representing them in reports 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.

Laura Molloy is currently the Chair of the Health Services Union Genetic Counsellor Committee and serves on the ASGC Award Committee, where she is responsible for working on genetic counsellor award structures across Australia.

Laura and Kathleen both have casual appointments as lecturers with the University of Technology, Sydney for the Master of Genetic Counselling course. Kathleen is continuing in 2025 as the Chair of the HGSA Professional Issue Committee for genetic counsellors and Chair of the Professional Complaints and Concerns Committee. 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.

On 12 November, the genetic counsellor team from RPA Hospital hosted an education day for NSW genetic counsellors. The event was a great success, drawing over 100 attendees both online and in person. We had an excellent line up of speakers and all presentations were well received. To celebrate Genetic Counsellor Awareness Day (GCAD) on 14 November, the NSW HGSA branch generously donated cakes and drinks decorated with GCAD and DNA-themed designs for attendees.

Molecular Medicine

Whole exome sequencing for neuromuscular disorders: Annual review

Dr Anthony Cheong
Genetic Pathologist, IPM&B

Gene panel analysis based on whole exome sequencing (WES) data at Concord Hospital's Molecular Medicine Laboratory has highlighted this test as a leading diagnostic tool for neuromuscular disorders, providing an efficient and comprehensive approach to genetic analysis. With the introduction of Medicare-funded testing in Australia in late 2022, access to WES has expanded significantly, further enhancing its role in clinical diagnostics. The flexibility of WES allows for tailored gene panels, which can be adjusted to meet specific clinical needs.

Our laboratory manager, Dr Danqing Zhu conducted a review of WES testing over the one-year period between 2023-2024. Gene panels that are included for review are listed in Table 1. These gene panels include clinically relevant, validated genes selected from public databases, literature, and customer requests.

Table 1: Panels for WES neuromuscular gene analysis

Amyotrophic Lateral Sclerosis (ALS)
Ataxia
Comprehensive Neuromuscular Disorders
Congenital Myasthenic Syndromes
Neuropathy
Dementia
Dystonia
Custom panels for other neurologic disorders with specific phenotypes
Hereditary Spastic Paraplegia (HSP)

Over the one-year period, the laboratory analysed 476 cases, identifying 167 patients with pathogenic, likely pathogenic, or clinically relevant variants of uncertain significance (VUS) (Figures 1 and 2).

The diagnostic yield was 35.2%, which aligns with findings in the literature. The majority of pathogenic variants were identified through the comprehensive neuromuscular gene panel and the neuropathy panel, which together accounted for 70% of the diagnoses.

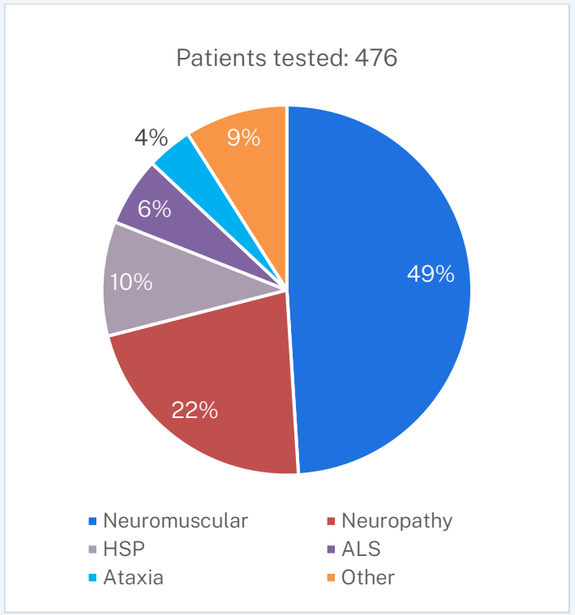


Figure 1. Percentage of requests for each panel from the patients tested.

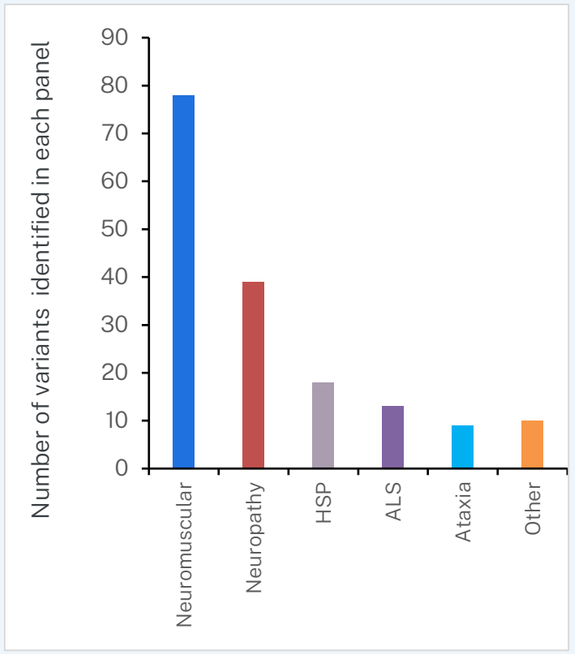


Figure 2. Numbers of pathogenic/likely pathogenic/clinically relevant VUS identified in each panel.

Clinical impact of WES testing at Molecular Medicine Laboratory

The identification of pathogenic variants has had a significant impact on patient management. Some of the identified conditions are now treatable, for example, a wheelchair-bound patient was able to mobilise independently after treatment with salbutamol syrup, following the diagnosis of congenital myasthenia syndrome with compound heterozygous pathogenic variants in *COLQ*. Ataxic patients with previously undiagnosed biotinidase (*BTD*) deficiency now receive biotin replacement to alleviate progression of symptoms.

In motor neuron disease cases, the detection of *SOD1* pathogenic variants provide patients with opportunities for enrolment in clinical trials. The implementation of WES testing has also provided opportunity for the laboratory to contribute to the current knowledge base. The laboratory submitted 33 variants to ClinVar, 17 of which were first-time submissions. Additionally, variants previously reported were resubmitted where new phenotypic associations were identified or when the variant had a conflicting classification in ClinVar (Table 2).

Table 2: New ClinVar submission resulted from testing

Panel	Gene	Reference	Variant	Classification
ALS	*NEK1*	NM_001199397.3	c.1414C>T (p.Arg472Ter) c.1804C>T (p.Gln602Ter)	Likely pathogenic Likely pathogenic
	GRN	NM_002087.4	c.1435C>T (p.Gln479Ter) c.502_503insT (p.Gly168fs)	Likely pathogenic Likely pathogenic
	SOD1	NM_000454.5	c.34G>T (p.Asp12Tyr)	Likely pathogenic
Neuropathy	*HPDL*	NM_032756.4	c.1066G>C (p.Ala356Pro)	Likely pathogenic
	DHTKD1	NM_018706.7	c.2546A>T (p.Glu849Val)	Uncertain significance
Neuromuscular	*DES*	NM_001927.4	c.89_109del (p.Leu30_Pro36del)	Uncertain significance
	SLC6A1	NM_003042.4	c.994del (p.Met332fs)	Likely pathogenic
HSP	*KIF5A*	NM_004984.4	c.788G>A (p.Gly263Asp) c.129+1G>A	Likely pathogenic
	SPAST	NM_014946.4	c.532C>T (p.Gln178Ter) c.911del (p.Pro304fs)	Pathogenic Pathogenic
	CYP7B1	NM_004820.5	c.1162C>G (p.Arg388Gly)	Likely pathogenic
CMS	*GFPT1*	NM_001244710.2	c.1526T>C (p.Met509Thr)	Likely pathogenic
	COLQ	NM_005677.4	c.1026C>G (p.Asp342Glu)	Likely pathogenic
	CHRNE	NM_000080.4	c.1052C>G (p.Pro351Arg)	Likely pathogenic

Overall, the most frequently identified pathogenic variants occurred in the following genes (Figure 3):

- Neuropathy Panel: PMP22, GJB1, HSPB1, MPZ, VCP
- Neuromuscular Panel: NOTCH3, PYGM, GAA, DYSF, RAPSN, CYP7B1
- Spastic Paraplegia Panel: SPG7, SPAST
- ALS Panel: SOD1

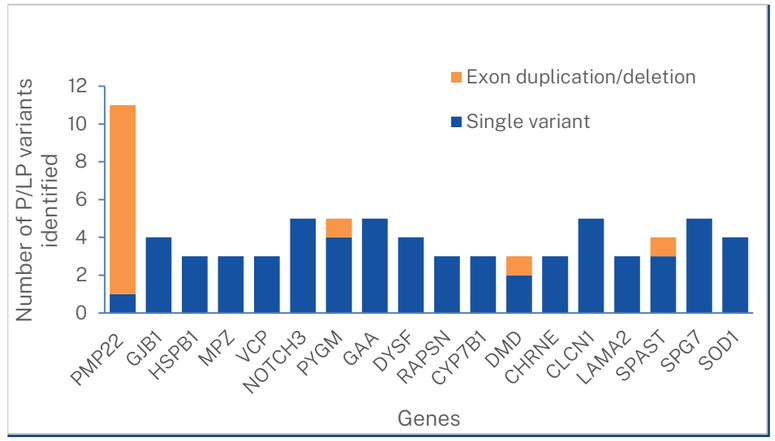


Figure 3. List of common genes with pathogenic/likely pathogenic variants (P/LP) detected from data review.

Pharmacogenomics

Dr Hugh French
Genetic Pathologist
Department of Medical Genomics

Pharmacogenomic (PGx) testing is an application of precision medicine that can guide medication selection and correct medication dosage depending on a patient's genotype (PMID: 36259142).

Ensuring that medications are prescribed and dosed correctly for an individual based on results of genotyping of relevant genes, to help patients remain within the therapeutic index and avoid adverse drug reactions, is important to ensure the safe and efficacious use of medicines (PMID: 36259142).

Patients identified by genotyping as unable to metabolise a medication, are able to reduce the chance of an adverse drug reaction with precision targeted therapy. These range from mild in severity, to very severe adverse drug reactions with the potential to result in admission to intensive care or in extreme cases, death (PMID: 36259142).

The Royal College of Pathologists of Australasia (RCPA) Pharmacogenomic Indications in Australia have recently been published with the recommendation of PGx testing in specified clinical settings. Ideally this should occur prior to exposure to a drug, known as pro-active testing. Testing may also be performed reactively after a drug has caused side-effects or has not had the expected therapeutic response.

This guideline has been endorsed by other colleges and professional bodies including The Royal Australian and New Zealand College of Psychiatrists and The Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Tailoring prescribing decisions to an individual's genetic background before prescribing the medications at a standard dose is standard of care for the included drugs where PGx testing is recommended. A list of these is available on the RCPA website. Drug gene pairs where PGx testing may be considered or is available are also listed.

Broadly there are four outcomes when a patient is prescribed a drug for the first time. The new drug may have clinical benefits and no adverse side effects as intended.

However, the drug may have clinical benefit but adverse side effects, clinical benefit but side effects requiring the drug be ceased, of no clinical benefit or adverse side effects as the drug has no effect (PMID: 30010447).

Precision dosing is of increased importance for medicinal products with a narrow therapeutic index and may be informed by genotyping that predicts poor, normal or rapid metaboliser status to ensure clinical benefit and avoid adverse drug reactions (PMID: 30010447).

A well evidenced example of PGx guided therapy is MBS eligible testing for *TPMT* and *NUDT15* (MBS#73327) to prevent thiopurine toxicity. While the MBS item only requires testing for *TPMT* variants, the addition of screening for variants in *NUDT15* allows detection of variants common in East Asian ancestry groups (PMID: 35931343).

PGx testing for *DPYD* genotyping is recommended to predict fluoropyrimidine-induced toxicity and has been recommended for MBS subsidies by MSAC; details of this application are available on the MSAC website. A pilot of NATA accredited *DPYD* genotyping has been commenced at the Department of Medical Genomics at RPA Hospital to inform the prescription of capecitabine and fluorouracil as recommended by the RCPA Pharmacogenomic Indications in Australia and eviQ guidelines (available on the Cancer Institute of NSW website).

Similarly adverse drug reactions to irinotecan are common in patients with Gilberts syndrome, an otherwise benign condition, caused by variants in *UGT1A1*. eviQ and DPWG guidelines suggest that dose reductions be considered in patients with Gilberts syndrome (PMID: 36443464).

Clopidogrel, an antiplatelet medication that prevents blood clots in patients is commonly prescribed after heart attacks or strokes, with *CYP2C19* testing recommended prior to prescription of antiplatelet therapy. Prescription of alternative therapies where appropriate is recommended, to prevent treatment failure (see further here).

The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group recommend adjusting the voriconazole dosing based on the *CYP2C19* genotype, accordingly the RCPA recommends adjusting the voriconazole dosing regimen based on *CYP2C19* genotyping results (PMID: 39246651). In conjunction with therapeutic drug monitoring, dosages may be optimally adjusted to ensure patients remain within a narrow therapeutic window (PMID: 34937141).

Cystic fibrosis has historically been managed by treating the impact of the disease on end-organs, such as lungs, due to long-term sequelae of the disease. Recently, however, PBS subsidised targeted treatments are available based on the specific genotype and class of CFTR disease-causing variants identified during diagnostic CFTR sequencing (see further here). These include medications elexacaftor, tezacaftor and ivacaftor which are prescribed, either alone or in combination, to cystic fibrosis patients with targetable variants such as F508del, G551D and class III gating mutations (PMID: 37574040, 35153502).

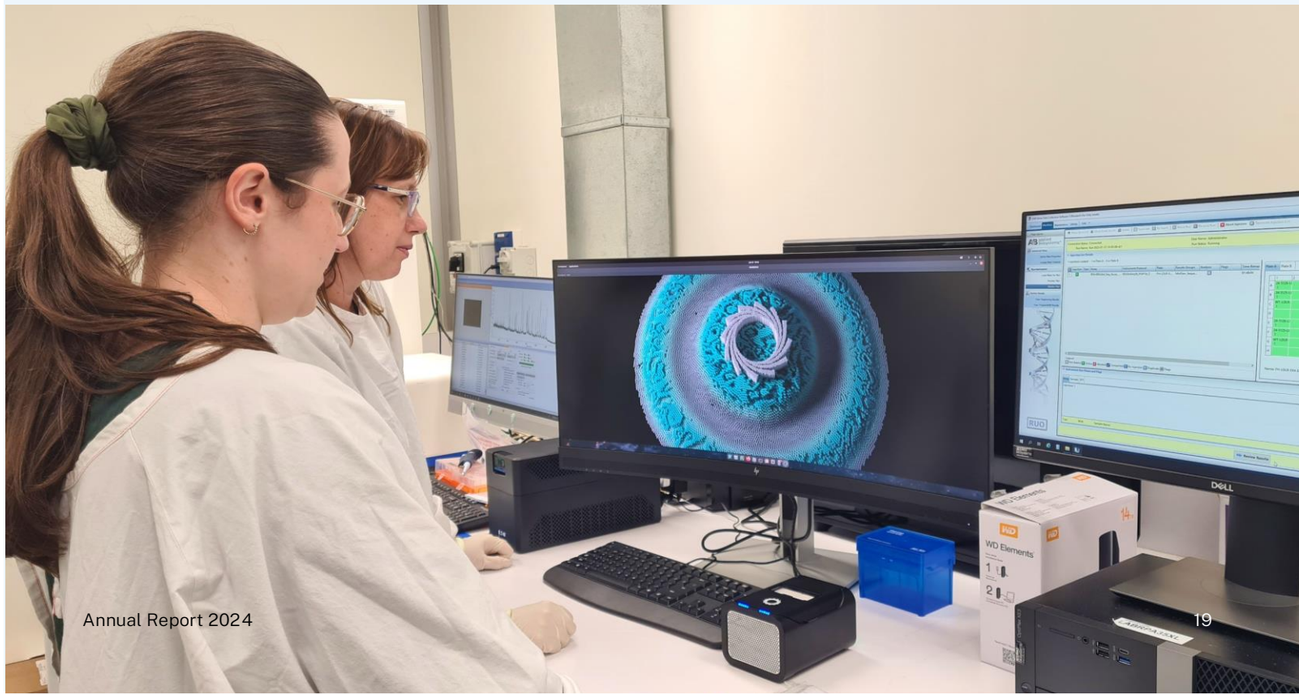
PGx testing is also applied to guide treatment and warn prescribers about risks of toxicity when prescribing medications such as abacavir and carbamazepine.

Patients with the HLA-B*5701 genotype are at risk of a hypersensitivity reaction from abacavir and should avoid the medication (PMID: 24561393).

Accordingly, testing for HLA-B*57:01 to guide abacavir prescription is eligible for rebated testing by Medicare (#73323). Similarly, carbamazepine genotype guided prescribing is recommended as HLA-B*15:02 is strongly associated with greater risk of Stevens-Johnson syndrome and toxic epidermal necrolysis (PMID: 29392710).

An important PGx gene, *CYP2D6,* is involved in the metabolism of around 25% of medications, including medicines routinely prescribed by psychiatrists, such as atomoxetine, doxepin, nortriptyline and paroxetine. Genotyping of *CYP2D6* is complicated by structural variants such as hybrid genes and duplications, and a precision medicine approach that captures rare variation in this gene through the utilisation of long-read sequencing, such as by Oxford Nanopore or PacBio platforms, may improve prescribing practices (PMID: 39262167).

The current paradigm of testing as recommended by the RCPA is genotyping of specific genes when prescribing a drug with a high level of evidence, in line with MBS eligible PGx testing items. However, in the future, panels of multiple PGx genes may become standard of care, as even a four gene panel found at least one actionable PGx variant in 96% of Australians (PMID: 30191366).



Bioinformatics

Dr Abdul Baten
Genomics Bioinformatician, IPM&B

Pharmacogenomics report generation and automation

Pharmacogenomics (PGx) leverages advanced genomic testing to identify genetic variants, hybrid alleles, and copy number variations in genes that play a critical role in the metabolism of drugs used across various medical specialties. This field represents a transformative approach to personalised medicine, enabling the prediction of an individual's risk of adverse drug reactions and their therapeutic response to medications based on unique DNA genetic variations. Genetic variants can result in enzymes with altered functionality, leading to significant clinical outcomes, such as drug toxicity, adverse reactions, or therapeutic inefficacy. By understanding these genetic variations, healthcare providers can tailor drug selection and dosing to optimize treatment outcomes and minimise risks.

Central to PGx are the cytochrome P450 (CYP) enzymes, a large family of proteins encoded by over 50 genes. These enzymes are integral to the metabolism of many medications, breaking down drugs into active or inactive forms and thereby influencing their efficacy and safety. In addition to the cytochrome P450 family, the *DPYD* gene, which encodes the enzyme dihydropyrimidine dehydrogenase, is gaining prominence in PGx.

The most relevant variants in genes implicated in drug metabolism pathways can be tested by pre-designed (VeriDose Core and VeriDose CNV) and custom (PGxOnco) Mass iPLEX Array assays from Agena Biosciences. Briefly, samples undergo multiplexed PCR reactions, followed by iPLEX Pro single base extension reactions. The extension products are dispensed onto a support matrix, SpectroCHIP Array, and data acquisition performed on the MassARRAY MALDI-TOF mass spectrometer. Data are acquired on the MassARRAY Analyzer 4 and processed using MassARRAY Typer and a results report generated by PGx Report v4 software, showing SNP and CNV results in a single report file.

While the Typer software provides a robust platform for data analysis, the current workflow involves a labour-intensive step where data from multiple sources — including genetic results, patient demographic information, and clinical annotations — must be manually collated and entered into the final clinical report. This manual process is not only time-consuming but also prone to transcription and entry errors, potentially compromising the accuracy of the reports.

To address this inefficiency, an in-house program with graphical user interface was developed that fully automates the collation and integration of data from various sources into a comprehensive clinical report. This software streamlined the entire process, eliminating the need for manual data entry and significantly enhancing both accuracy and efficiency. This program required three sets of information selected by a user before it generated a word file report:

- Typer CSV report file
- PGx template file
- Patient demographic information
- Output directory (where generated word reports are stored).

Once the information is submitted to the automatic report generation software by clicking on the "Generate PGx Reports" button, the reports are automatically created and saved in the specified output directory folder (Figures 1 and 2). This program can automatically generate reports for hundreds of patients in one click given all the information is provided.

Two additional accessory programs have been developed to streamline the automation process.

- **Barcode generator**: This program generates barcodes for web links, such as the eviQ prescribing recommendation site. Instead of relying on a traditional web link, the barcode allows users (typically clinicians) to quickly scan and access the link using a mobile or handheld device, eliminating the need for a computer to browse the information.

- **Word to PDF converter**: This program efficiently converts hundreds of clinical reports into PDF format instantly, saving significant time compared to converting each report individually. All reports are required to be uploaded in PDF format, making this tool an essential part of the workflow.

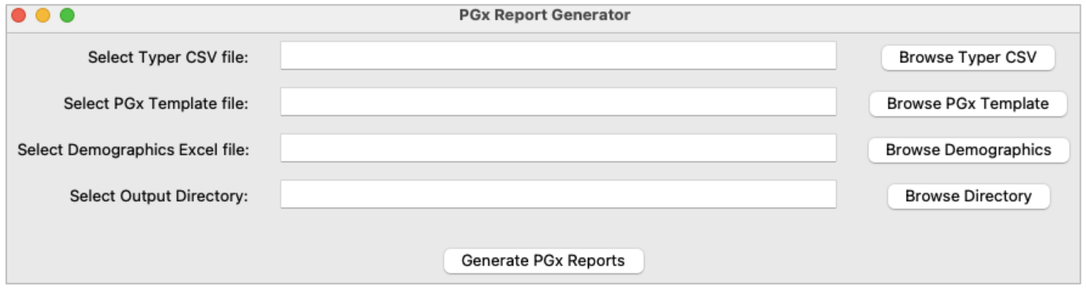


Figure 1. Graphical User Interface to upload the Typer results and related files.

NSW GOVERNMENT Health Pathology

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PHYSICIAN AND PATHOLOGIST INFORMATION

Name:
Address:

PATIENT INFORMATION
Name: XX, Xx
DOB: XX/XX/XXXX
Gender: X
Our Lab No: XXX
Sample Type: Blood
Received Date: 17/12/2024
Reference No: XXX

PHARMACOGENOMICS REPORT ..... DPYD GENOTYPING (10 alleles)

CLINICAL INDICATION for testing:

RESULTS:

Sample	DPYD
XXXX	*1/*1

PRESCRIBING RECOMMENDATIONS: This patient has a **normal metaboliser DPYD genotype**. There are no changes to the starting therapy dose or dose titrations for fluoropyrimidine usage recommended by eviQ guidelines in the above patient. *Note limitations of the DPYD genotype test below.*

eviQ PRESCRIBING RECOMMENDATIONS: This patient has an **abnormal metaboliser DPYD genotype.** A change in starting therapy dose and dose titration is recommended by eviQ.

Scan the QR code to view on your iphone in landscape format the eviQ recommendations (eviQ guidelines issued 24 February 2023).
Note limitations of the DPYD genotype test below.

COMMENTS

- Patients should not use these results to stop, change or alter dose of a medication unless changes are recommended by their medical practitioner.
- eviQ refers to enzyme (DPD) phenotyping which measures enzyme activity. A comparison between the DPD enzyme activity test (phenotype) to the DPYD gene (genotype) test is not provided although eviQ notes that treatment options based on the DPD enzyme test are more difficult to make compared to the DPYD genotype test. Where the DPYD gene test is *1/*1 or "normal" but the patient cannot tolerate fluoropyrimidine therapy, consideration should be given to the DPD enzyme activity test because false negative results are possible with DPYD genotyping (see Limitations).

Figure 2. Model PGx report generated by the program.

Cloud-based bioinformatics analysis server

Precision medicine focuses on targeting specific genetic mutations with specialised treatments, enabling more effective and personalised care. In the context of cancer, a disease caused by mutations that drive uncontrolled cell growth, this approach requires identifying these mutations through genetic testing. By analysing DNA or RNA from tumour or blood samples, next generation sequencing (NGS) generates vast datasets that must be processed swiftly using bioinformatics analysis pipelines to guide appropriate treatment decisions.

To enhance efficiency, we collaborated with the District's Digital Health & Innovation (DH&I) team to implement cloud-based analysis pipelines. This solution enabled scientists to flexibly launch and resize virtual machines in Microsoft Azure, depending on sample volume, minimising IT support needs and optimising resource utilisation. This ensured all samples were processed simultaneously, expediting the reporting of genetic variants and enabling timely cancer treatments. With the support of DH&I and NSW Health Pathology IT, Archer bioinformatics servers for the Medical Genomics and Haematology departments were upgraded from version 6.2 to 7.2, introducing new features. These servers have been rigorously tested and validated for production use. Moreover, Archer pre- and post-analysis hooks were rewritten to ensure compatibility with the updated version, streamlining the analysis process.

Whole exome sequencing: ensuring sample integrity check

The RPA and Concord laboratories have achieved NATA accreditation for providing diagnostic whole exome sequencing (WES) services. To maintain the highest standards, a bioinformatics workflow has been established to manage quality control (QC) for raw sequencing reads, binary alignment and mapping (BAM) files, and variant call format (VCF) files. Additionally, a robust process is in place to ensure DNA sample integrity and sequencing data reliability.

Once genotype calls are generated using the Agena Custom Exome QC Panel, they are cross verified against the exome sequencing data. To streamline this process, a bioinformatics workflow has been developed, combining command-line utilities and a graphical user interface.

The workflow performs the following key functions – extracts genotype calls from the alignment BAM file, compares these genotype calls with those from the QC panel (Agena) and generates a detailed report summarising results, highlighting issues such as sample mislabeling, altered samples, incorrect genotype calls, or potential discrepancies.

In a recent enhancement, the sample QC code was updated from Bash to Python, making the system more robust and adaptable. Further work is ongoing to simplify and refine the workflow, aiming to enhance usability and efficiency while maintaining rigorous QC standards.

Bioinformatics and AI educational initiative

The integration of Artificial Intelligence (AI) and machine learning is transforming healthcare, making it essential for health professionals to understand these technologies. Collaboration between technologists and healthcare professionals is crucial to address complex challenges, ensuring AI applications meet clinical needs and ethical standards. By equipping doctors, scientists, and other professionals with AI knowledge, they can contribute to the development and refinement of these tools.

To promote education in bioinformatics and AI, IPM&B partnered with the Biomedical Informatics and Digital Health (BIDH) department at the University of Sydney to develop educational initiatives and recruit potential research students. As part of the IPM&B seminar series in 2024, two presentations highlighted bioinformatics and AI. Building on this momentum, a parallel bioinformatics and AI seminar series will launch in 2025, further advancing training and awareness in these critical fields.

Additionally, Dr Abdul Baten was part of the organising committee for the Symposium on Bioinformatics Excellence and Innovation (SBEI24) at the 2024 annual Australian Bioinformatics and Computational Biology Society conference. The symposium focused on applications of bioinformatics in industry.

Figure 3. #SBEI24 event program.

Pictured: #SBEI24 event.

Precision Medicine Consumer Group

Dr Alan McPhail
IPM&B Consumer Representative

The activities of the Precision Medicine Consumer Group provided opportunities for consumer involvement in the development of precision medicine models of care and research. The aims in 2024 were to:

- highlight to health consumers (patients, carers, family and community members) the opportunities presented by precision medicine
- provide education, support and networking opportunities for health consumers who have an interest in being involved in precision medicine (clinical care and research)
- provide opportunities for the consumer group members to contribute to precision medicine research proposals and clinical care proposals.

The group was supported through a combination of three virtual meetings, one in-person meeting, suggested reading materials, and events like *ReConX – Building Researcher and Consumer Connections*. This event was hosted by Sydney Health Partners and the Sydney Knowledge Hub, with support from Health Consumers NSW. Additionally, regular email communication helped keep the group engaged.

The 2024 meeting program of the Precision Medicine Consumer Group brought together experts, researchers, and consumers to discuss the latest advancements in precision medicine, including pharmacogenomics, oncology, and familial hypercholesterolemia.

The key discussions and outcomes from the series of virtual and in-person meetings were as follows:

- **Pharmacogenomics (PGx)**: The program kicked off with an update on Professor Tim Lambert's research into PGx and mental health.

The session also focused on the implementation of PGx into clinical care at RPA Hospital, specifically in oncology, cardiovascular care, and metabolomics. This meeting highlighted the growing potential of PGx in personalising treatments and improving patient outcomes.

- **Precision oncology**: Professor Bing Yu led an engaging session on the advancements in somatic cancer DNA testing at RPA Hospital. The discussion centred around the PrOSPeCT program, Australia's largest cancer genomics initiative, which alms to revolutionise cancer care by using genetic insights to inform treatment strategies. The meeting underscored the importance of precision oncology in offering targeted therapies based on genetic markers.
- **Familial hypercholesterolaemia (FH)**: Professor David Sullivan presented a grant-funded project focused on improving the understanding of cascade screening for FH among primary healthcare providers. Consumer feedback was sought regarding the FH Lifelong Management App, which is designed to support individuals managing FH throughout their lives. The session also highlighted the work of FH Australia – a charitable foundation advocating for families affected by this genetic condition.
- **2024 wrap-up**: The final meeting of the year look place in person at RPA Hospital, where attendees were updated on the implementation of PGx testing at the hospital. A Consumer Rep roster for the PGx Expert Recommendation Panel was introduced, and feedback was gathered on PGx reporting formats. The session concluded with a thank-you morning tea, celebrating the contributions of all those Involved in these Important initiatives.

Throughout the year, the meetings facilitated collaboration between precision medicine experts and consumers. The consumers appreciated the learning opportunities, the chance to ask questions, and are eager to be involved in upcoming projects. We look forward to continuing these discussions and seeing further progress in consumer involvement in research in 2025.

Innovation

Innovation

Professor Ron Trent
Director, IPM&B

Multi omics in precision medicine

The building blocks for precision medicine are initiated by a sophisticated understanding of each individual, incorporating genetic and other measurable factors, ideally within the context of environmental interactions. From this input, a profile is established which identifies important interventions, or the effector component for precision medicine.

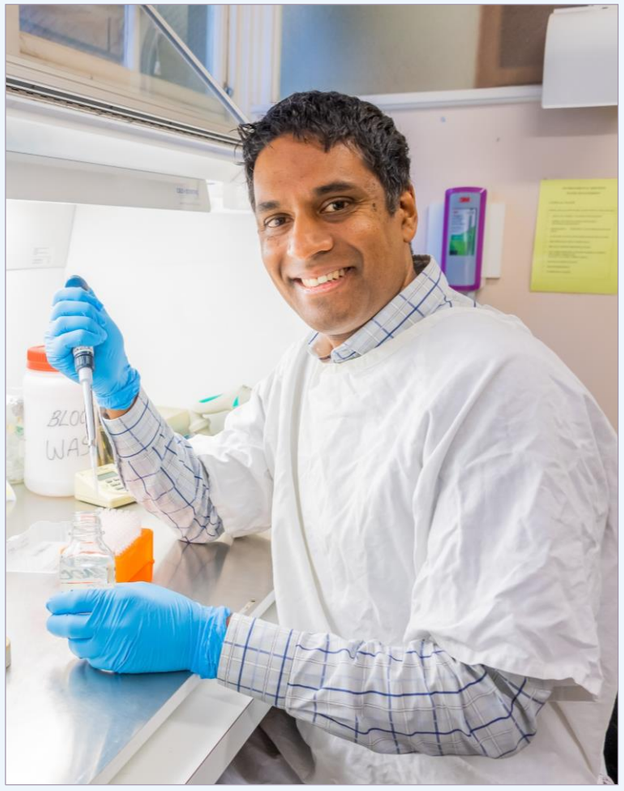
Traditionally, information based on genomics has been the source of the initial input, although other “omics” are now being considered. In 2024, the precision oncology group in the Department of Medical Genomics, led by Associate Professor Bing Yu, integrated transcriptomics with genomics to create a more advanced tumor profile, opening up new therapeutic options for treating advanced cancers.

If a dual omics approach is valuable, why not a multi omics approach? This was the central theme of the IPM&B's 2024 Annual Scientific Meeting, sparking numerous discussions throughout the year on metabolomics and proteomics. Although both these omics are actively pursued in research, they are yet to cross the translational bridge into clinical care. The role of a limited metabolomics approach in PGx was of particular relevance since the ability to measure metabolites through therapeutic drug monitoring provides a superior analytic approach to gene testing alone.

Collaborations with Digital Health & Innovation

With the shift from in-house computing hardware to cloud computing, the availability of local bioinformatics and ICT experts diminished. At the same time, growing concerns about privacy risks and the need for enhanced cyber security with cloud computing highlighted the need for local expertise to ensure safe and efficient access to a digital network protected by a firewall. The situation became critical when even "simple tasks," like software updates, began to disrupt the reliable operation of genomic analytic platforms. Amidst this complexity, the IPM&B was fortunate to have the support of the District's Digital Health & Innovation (DH&I) team. Their experts took the time to understand our processes and the issues we were facing. One key example was when a vital analytic platform, for example Illumina's MiSeq, would fail if a scheduled antivirus update coincided with a routine run, resulting in failed runs and delayed results. The frustration was widespread. In the end, the problem was resolved with a dedicated isolated network, better communication around planned updates, and an expert on hand to assist with any disruptions during runs.

Through our many informal and formal meetings with DH&I, we gained a deeper understanding of the importance of cyber security and the NSW eHealth’s Privacy and Security Assurance Framework (PSAF) requirements. Before DH&I’s involvement, PSAF seemed to restrict any new developments in digital health. Now, we not only understand why certain actions aren’t possible, but also know what needs to be done to advance digital initiatives while maintaining cyber security. The IPM&B is very grateful for the support of Alex Wagstaff, the Head of DH&I. While she is seconded to the SDPR, we also appreciate the availability and enthusiasm of David Norwood, who is serving as Acting Head. The professionals in DH&I have taught us a lot and we expect the learning curve will continue to grow as eHealth initiatives demand greater compliance and accreditation in the digital space. We were also impressed by DH&I's vision for AI in clinical care and look forward to collaborating with Marc Pelusi from DH&I to advance the applications of AI in precision medicine.



Pictured: Associate Professor Kishore Kumar.

Mainstreaming with genomics champions

In a short period, the applications of genomic medicine have made substantial progress in medical research strategies and have contributed to the development of more innovative clinical care models. The latter increasingly relies on genomic testing (whole exome based or via small to large gene panels) to enhance the diagnostic capability particularly for relatively uncommon disorders. Medicare has helped here with an earlier reluctance to provide new MBS-funded genomic tests now changing as clinical utility can be demonstrated via rigorous health technology assessment processes. The availability of gene panels for cardiac disorders such as cardiomyopathy or arrhythmias has enabled precision medicine strategies to be implemented more effectively. In this rapidly progressing field, it is a concern to hear that medical practitioners including specialists might not have the genomic knowledge to obtain consent, understand what tests can be ordered or even what the results mean. However, the solution is not to bypass them but to ensure that they can upskill to enable genomic medicine to become a part of their everyday clinical and research practices. Hence, NSW Health has, as part of its Genomics Strategy the requirement for mainstreaming to expand the understanding and use of genomics into all clinical disciplines (which will then facilitate the use of genomics in research).

One way to progress mainstreaming is to identify discipline-specific “genomics champions” and work closely with them including mentoring, when required, to upskill in all facets of genomic medicine. Once a genomics champion has attained the skills, that individual then provides the leadership and mentoring for others within the same discipline.

The IPM&B has been working with the RPA Department of Respiratory Medicine and Concord Hospital’s Neurology Department to support genomics champions in these disciplines. The IPM&B will expand these activities in 2025 to other medical departments across the District.

In 2024, the IPM&B’s November e-News highlighted the work of Associate Professor Kishore Kumar, a senior neurologist at Concord Hospital and a genomics champion in the area of neurogenetics.

Andrology and precision medicine

Dr Veena Jayadev
Head, Department of Andrology, Concord Hospital

The Andrology Department, together with its co-located Andrology laboratory, has over 30 years expertise in diagnosing and treating rare and uncommon diseases such as disorders of sexual differentiation (DSD) and congenital hypogonadotropic hypogonadism. Due to being the only public andrology service in Australia, we receive referrals and requests for advice from around the nation. This has led to being in a unique position to understanding the genetic basis of these diseases.

Genetic testing has improved early diagnosis resulting in reducing distress at diagnostic uncertainty and has allowed genetic counselling for pregnancy planning for the affected individual and their relatives.

This is exemplified by a recent publication Molecular mechanism of androgen receptor mutation in multigenerational mild androgen insensitivity syndrome. Androgen insensitivity syndrome (AIS) is due to mutations in the androgen receptor (AR) and creates a spectrum of presentations based on AR function, with the mildest impairment creating mild androgen insensitivity syndrome (MAIS), where undefined molecular mechanism and subtle clinical features leave it less understood and under diagnosed.

More than 1,000 AR mutations have been identified, including over 600 germline mutations, making it the most common DSD. MAIS is the least well described form of AIS with its relatively subtle phenotype rendering it under diagnosed, so its true prevalence is unknown.

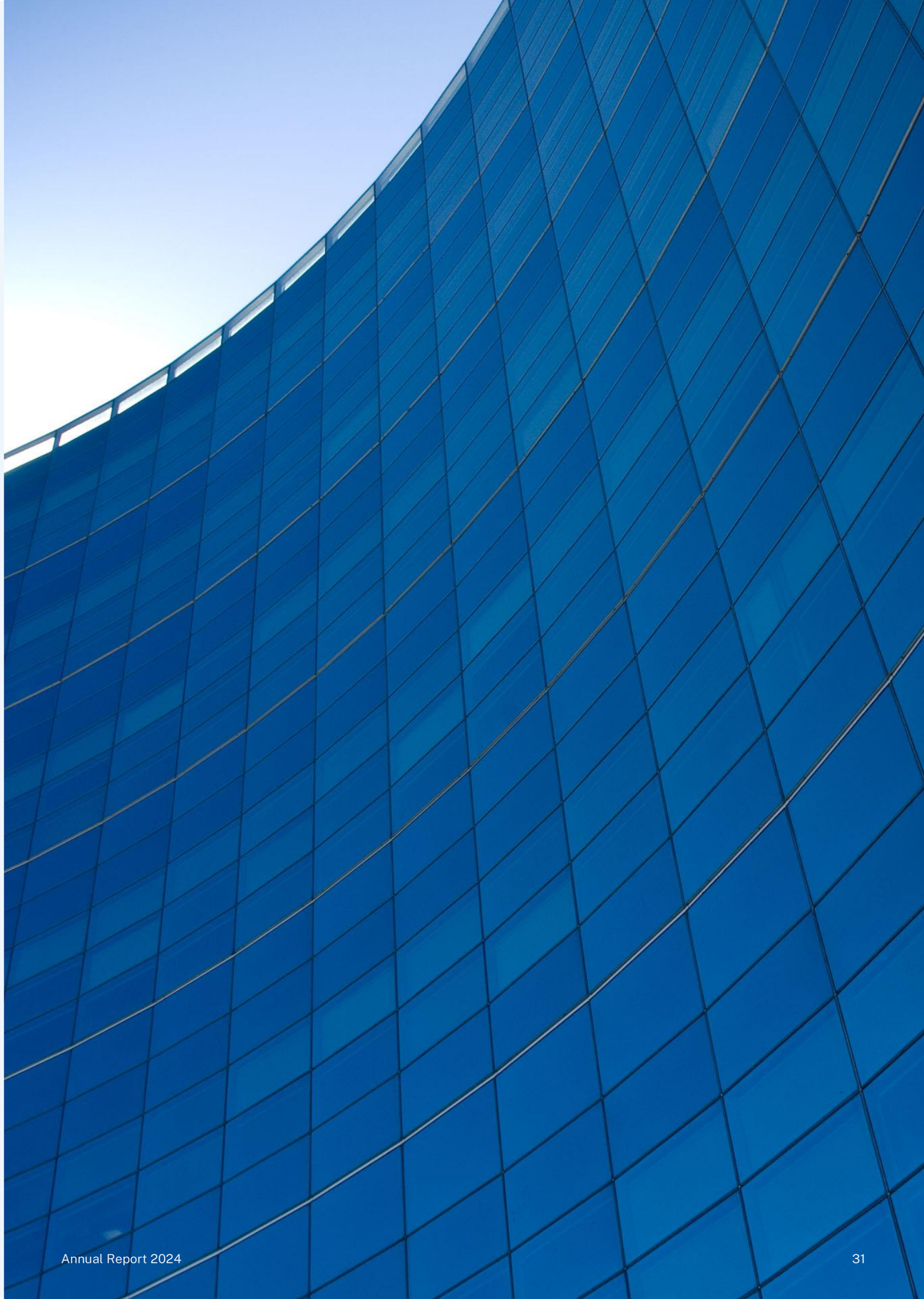
In the above publication we described a family of three cases of MAIS over a six-generation family pedigree. Genotyping confirmed the mutation – a missense AR exon 8 mutation. This is known to cause an increased ligand dissociation rate in mutant AR in binding assays.

In silico modelling and in vitro androgen bioassay of the mutated AR was used to identify its structural and physiological mechanism – the mutation weakens the closure energy of the “lid” of the ligand-binding pocket, allowing easier ligand dissociation from the binding site but with unimpaired in vitro androgen bioactivity.

High dose testosterone treatment may therefore be effective treatment. Genetic counselling allowed effective prediction of MAIS risks in progeny for carrier and non-carrier sisters. We can also offer earlier diagnosis and tailored management to people who present with subtle phenotypes.

The genetics of congenital hypogonadotropic hypogonadism is another area where we are expanding global knowledge on the genetics of an understudied disease. While the severe phenotype may present at birth with micropenis, it often presents with a delayed or stalled puberty, or with infertility and/or hypogonadism in adulthood. In collaboration with Dr Anthony Cheong and the Concord Molecular Medicine laboratory, we have found a genetic diagnosis in approximately 30% of patients and another 20% with variants of uncertain significance, which are entered into an international database. The whole exome sequencing is stored, able to be reanalysed at a later date, as bioinformatics advances and more pathological mutations are described. We are working to improve diagnostic effectiveness and efficiency through better understanding of the impact of genetic variants.

Patients are already seeing the benefits of genetic diagnosis, with pre- conception genetic counselling, as well as helping their children and relatives obtain earlier diagnoses, avoiding emotional distress and future uncertainty.



Research

Grants awarded

- A national platform for evaluation and integration of advanced analytics in the diagnosis of genetic disease.
  MRFF Genomics Health Futures Mission.
  Prof Marina Kennerson, CI.
  Funding $8million
- Developing a long-read nanopore sequencing platform for Indigenous genomics.
  Genomics Health Futures Mission.
  Dr Amali Mallawaarachchi, CIE.
  Funding $1million
- Establishing the Interstitial Lung Disease (ILD) Variant Curation Database.
  Centre for Research Excellence in Pulmonary Fibrosis.
  1 Jul 2024–30 Jun 2025.
  Dr Felicity Collins
- Establishing the Pulmonary Fibrosis Variant Curation Database.
  Pulmonary Fibrosis Australasian Clinical Trials (PACT) Network.
  1 Jan 2025–31 Dec 2025.
  Dr Felicity Collins
- Harnessing nanopore sequencing technology to improve diagnosis of human disease.
  Medical Research Future Fund.
  Assoc Prof Kishore Kumar, CI;
  Dr Amali Mallawaarachchi, CI;
  Dr Anthony Cheong, CI;
  Prof Ron Trent, AI;
  Dr Hugh French, AI.
  Funding $1million
- Implementation of ESR1 testing for the resistance variant detection from liquid biopsy using NGS. Industrial Grant from Stemline Therapeutics Switzerland GmbH.
  Assoc Prof Bing Yu.
  Funding $50,000
- 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
- KidGen National Kidney Genomics Program Genomics Health Futures Mission.
  Dr Amali Mallawaarachchi, CIF.
  Funding $3million
- Monogenic Parkinson's Disease Australia Initiative (MonoPDAus Initiative) – towards a precision medicine approach.
  Medical Research Future Fund.
  Assoc Prof Kishore Kumar, CIA;
  Dr Anthony Cheong, AI.
  Funding $2.95million
- Newborn Gen Seq Trail (Newborn Genomic Sequencing in screening: Therapy Ready and Information for Life).
  Medical Research Future Fund.
  Dr Anthony Cheong, CI.
- Developing precision therapies for Autosomal Dominant Polycystic Kidney Disease by uncovering novel molecular mechanisms.
  NSW Health Early-Mid Career Grant
  Dr Amali Mallawaarachchi, CI.
  Funding $500,000
- Solving the unsolved: long read sequencing patient RNA to guide identifying mutations causing CMT.
  CMT Australia Research Grant.
  Prof Marina Kennerson, CI.
  Funding $20,000

Publications

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- **Mallawaarachchi A**, Biros E, Harris T, Bennetts B, et al. Shaping the future of kidney genetics in Australia: proceedings from the KidGen policy implementation workshop 2023. Human Genomics (2024) 18(1).
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Education

Genomics webinars

A key activity in promoting the adoption of precision medicine is continuous education. Fortunately, the SLHD is strategically located to provide access to a wide range of seminars, workshops, formal teaching activities both onsite and through the affiliated University of Sydney, as well as various medical research institutes. Additionally, social media and the growth of educational websites have greatly expanded the availability of information. Post-COVID-19, the opportunities for webinars have also grown significantly. In this milieu the IPM&B has a formal teaching program in precision medicine which is based on a limited number of webinars per year, an annual scientific meeting and an occasional workshop. An overarching consideration in the education program is to avoid duplication or topics with less relevance to precision medicine. This does reduce the overall attendance numbers, which are closely monitored, but hopefully increases the relevance of the educational activities.

Attendees at these webinars were not consistently the same healthcare professionals or disciplines or organisations. This is probably to be expected as the topics were broad and not necessarily relevant to a universal audience. NSW Health's Agency for Clinical Innovation was a regular attendee (four webinars). Interest coming from a wide audience base might indicate that aspects of precision medicine are impacting across different models of clinical care.

Although allowing time for Qs and As, the downside of the webinar teaching strategy is lack of human-to-human contact and ability to develop collaborations. Hence, the 2024 Annual Scientific Meeting was specifically designated as a face-to-face activity with time set aside at the beginning to meet the speakers. A key measure of success for the ASM would be whether it led to the establishment of new collaborations.

Emerging biological therapies

presented by
Professor John Rasko

Implementation or PGx into clinical practice

presented by
Dr Sophie Stocker

Metabolomics & proteomics

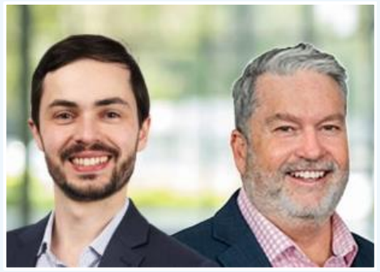
presented by
A/Prof David Sullivan &
Dr Jay Ramanathan

Health economics

presented by
Assoc Prof Michelle Cunich

Artificial intelligence for clinicians

presented by
Dr Thomas Hambly
& Marc Pelusi



Enhancing translational AI & bioinformatics

presented by
Dr Jason Li

Annual Scientific Meeting

Multi Omics

The theme for this half-day meeting was Multi Omics with the plenary speaker Professor Joseph Powell from the Garvan Institute of Medical Research discussing his internationally competitive work in single cell omics.

Two powerful technologies were illustrated in his talk – isolating single cells from tissues and then applying sophisticated bioinformatic analysis for generating genome, transcriptome and proteomics profiles. Joseph's team wrote an interesting paper titled Transitioning single cell genomics into the clinic in Nature Reviews Genetics in 2023. It is worthwhile reading to gain insight into where this approach is going.

Professor Anthony Linton from the Asbestos and Dust Diseases Research Institute at Concord showed how he, as a practising oncologist, could undertake research into mesothelioma, a cancer with a very poor prognosis, by studying the tumour's characteristics through multi omics.

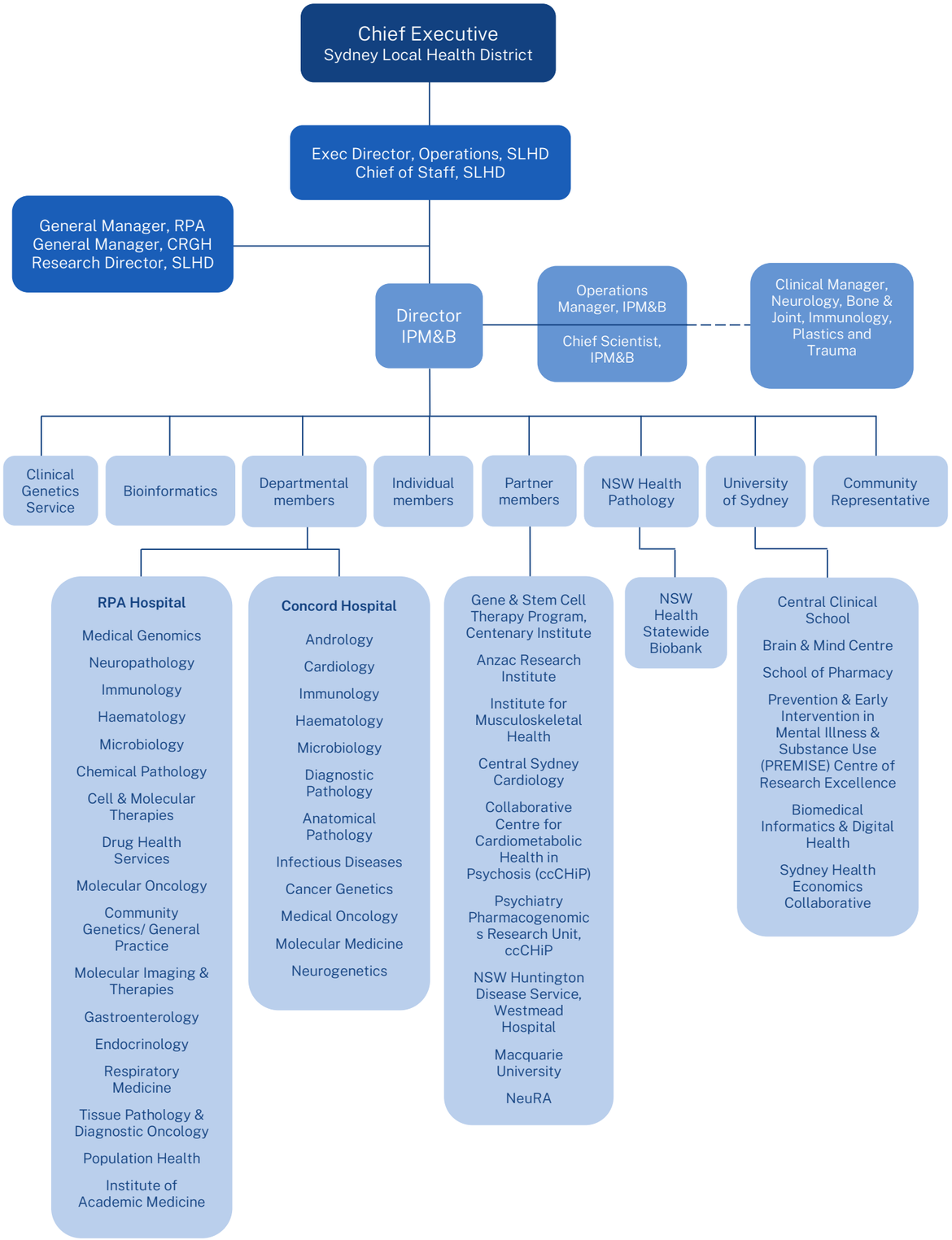
Professor Marina Kennerson from the ANZAC Research Institute at Concord showed why she has been successful with the highly sought after MRFF grant scheme. Her work through whole genome sequencing in hereditary neuropathies is showing the importance of the genome's 3D structure to explain disease causation.

Associate Professor Albert Lee, the final speaker from Macquarie University, shared insights into the challenges of translating proteomics for analysing post-translational modifications in degenerative brain disorders from research to clinical application. Nevertheless, the growing enthusiasm and resources at the Macquarie University campus offer optimism that significant discoveries will soon emerge.

Pictured: ASM presenters Professors Marina Kennerson, Joseph Powell, Ron Trent and Assoc Professor Albert Lee.

Organisation

Governance



Executive Leadership Team

Director
Professor Ron Trent
PhD, MB BS, BSc(Med) (Sydney), DPhil (Oxon), FRACP, FRCPA, FFSc, FTSE

Deputy-Director
Professor Marina Kennerson
BSc(Hons); MSc(Med); PhD

Deputy-Director
Professor Clement Loy
BA, MB BS, MMed(Clin Epi), FRACP, PhD

Operations Manager
Melissa Cole
BAppSci (Information)

Consumer Representative
Dr Alan McPhail
BAppSc, MEngSc, PhD

Strategic Advisory Council

Executive Leadership Team, IPM&B

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, USYD
Professor Stephen Twigg

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

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

Professor of RNA Biology, UNSW
Professor John Mattick

Head, Department of Immunology, RPA Hospital
Associate Professor Stephen Adelstein

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

Honorary Medical Officer, RPA Hospital
Dr Michelle S Lim

Registrar, Dept Medical Genomics, RPA Hospital
Dr Hugh French

Financial Report

2023-24 Financial Year

The below snapshot represents combined expenditure and revenue across all IPM&B cost centres. Approximately $2.9 million was employee-related expenses and a further $31,613 went towards Visiting Medical Officers (VMOs). Other operating expenses, including genetic testing sent to external laboratories, consumables, equipment repairs and replacement totaled $211,638. Our own-source revenue included $22,761 from patient fees.

Actual expenses	**$**	**%**
Employee Related	$2,991,315	91.76%
VMOs	$31,613	0.97%
Goods & Services	$211,638	6.49%
Repairs, Maintenance & Renewals	$25,238	0.77%
Total Expenses	**$3,259,804**	**100.0%**

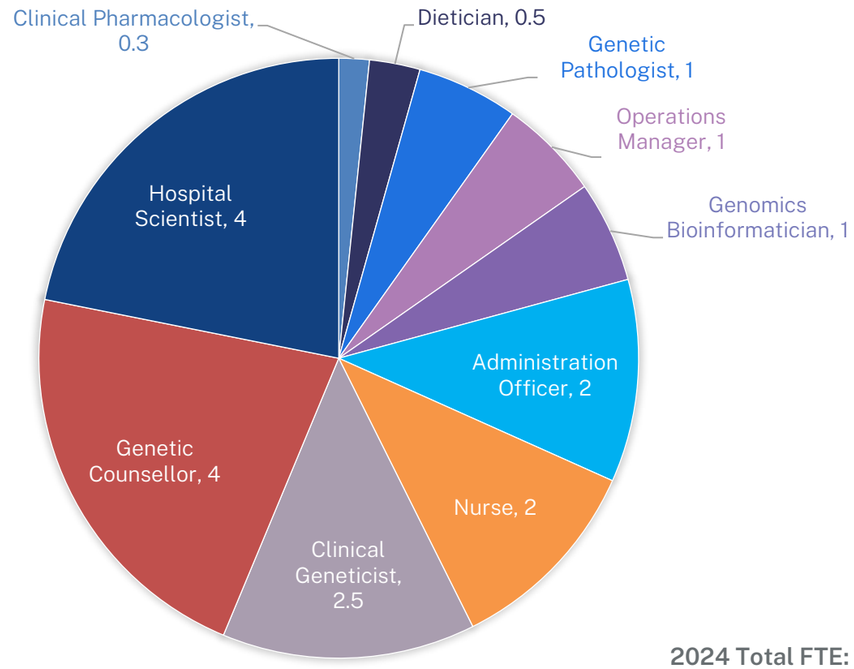
Actual revenue	**$**	**%**
Patient fees	$22,761	100.0%
Net Cost of Services	**$3,237,043**	**100.0%**

Government contributions	**$**	**%**
Crown Acceptance	$104,819	100.0%
Year Total Result	**$3,132,224**	**100.0%**

Source: Sydney Local Health District Year Total Financial Reports the year ended 30 June 2024.

Our Staff

Administered staff — FTE profile



2024 Total FTE: 18.3

New appointment

Dr Jay Ramanathan was appointed Staff Specialist in Clinical Pharmacology in January 2024, following his previous role as a Visiting Medical Officer at the Lipid Clinic at RPA Hospital.

Dr Ramanathan has made significant contributions to the therapeutic management of dyslipidemia, including playing a pivotal role in redesigning ambulatory care services at the Lipid Clinic. He is also an active member of several influential committees, including the Editorial Committees for Therapeutic Guidelines, Australian Prescriber, and the NSW Formulary Committee. Additionally, he serves on the Clinical Excellence Commission's Medication Safety Expert Advisory and Mortality/Morbidity Review Committees.

Beyond these roles, Dr Ramanathan is a member of the College's Policy & Advocacy Committee, a local examiner for the RACP, and a sub-investigator on multiple clinical trials focused on lipid disorders.

Future Directions

Professor Ron Trent
Director, IPM&B

Healthcare Services Plan 2024-2029

This plan outlines precision medicine as one of six key priorities for the District over the next five years. The development of precision medicine components was shaped through a series of workshops held in late 2023 and early 2024. These workshops, focused on specific disciplines, brought together health practitioners from RPA and Concord Hospitals to identify the needs for integrating precision medicine into their research and clinical practices. Consideration was also given to the Sydney Biomedical Accelerator, a joint District and University of Sydney initiative, which will feature a 220m^2 Precision Medicine Research Facility. This state-of-the-art facility will be a NATA ISO 15189 accredited laboratory, advancing cutting-edge research in precision medicine.

Pharmacogenomics (PGx)

Although the rollout of PGx has been slow and relatively low-key, it is expected that progress will accelerate once the various pilot programs in cancer treatment, the medical use of clopidogrel, and the particularly challenging PGx for mental health disorders are completed. Additionally, there are plans to further investigate how the *CYP2D6* gene can be better characterised for its complex CNVs, which are difficult to define using traditional PGx analytic technologies. The IPM&B is committed to ensuring that by 2029, all patients admitted to Sydney Local Health District facilities will have the option for a comprehensive PGx screen, providing personalised healthcare for prescription drugs.

Single Digital Patient Record (SDPR)

Upon assuming the Chief Executive role for the SDPR, Dr Teresa Anderson quickly invited leaders and experts from the District to join her team for the phased rollout. This presents a unique opportunity for the 9 million NSW residents who will use public hospitals and clinics, enabling the SDPR to offer comprehensive, lifetime health management. While the impact on clinical practice is still unfolding, the SDPR is expected to reach the District by late 2027. With all entries being digital, the volume of information will be vast, requiring AI to condense it into manageable components for healthcare professionals and patients. The SDPR will also enhance PGx's role in preventive medicine, making results accessible across the NSW public health system.

Champions for mainstreaming genomics

In late 2024, I visited Concord Hospital and the ANZAC Institute, where I learned about potential collaborations in precision medicine. I was particularly impressed by Professor David Handelsman and his team, who are incorporating genomics into andrology. The benefits of this approach will be interesting to follow in the coming years.

Educational opportunities

The 2025 webinar program will have two streams: one on traditional topics and another on AI in precision medicine. The ASM theme is still to be determined, with potential collaboration with the District's DH&I team to highlight AI's health implications. In 2024, I engaged with NSW Health's HETI, now incorporating the Centre for Genetic Education (CGE). This presents an opportunity for the IPM&B to collaborate with HETI and CGE to develop innovative, smartphone-accessible educational resources for precision medicine.

Unfinished business from 2024

The ongoing budget deficit will impact District services in 2025, potentially leading to changes in the structure, governance, and reporting framework for clinical streams and institutes at RPA and Concord Hospitals. The IPM&B's Strategic Advisory Council will need additional support for its strategic work, and senior executives within the IPM&B may require a more structured approach to advise the Director and support succession planning as precision medicine evolves over the next decade.

Our Stories

Research into genetic kidney disease at Sydney Local Health District

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

Kidney failure is associated with the lowest quality of life of any chronic disease and one of our highest healthcare expenses. Genetic kidney disease accounts for at least 10% of kidney failure in Australia. Genetic kidney diseases are varied, from cystic conditions such as Autosomal Dominant Polycystic Kidney Disease (ADPKD), glomerular disorders such as Alport syndrome, tubular channel-disorders such as Bartter and Gitelman syndromes and complement disorders such as atypical haemolotyic uremic syndrome. Advances in sequencing technologies have transformed our ability to diagnose patients with genetic kidney disease and Australia has been a world-leader in developing and implementing these techniques into clinical practice.

The KidGen Consortium is a national body of clinicians and scientists focused on improving outcomes in genetic kidney disease. The foundation of KidGen is a national network of Kidney Genetic MDT Clinics, running in all Australian states and territories. These clinics provide families with access to genetic counselling and diagnostic testing for genetic kidney disease and also links families with ongoing research studies, including genomic research for undiagnosed patients and clinical trials. Over the last ten years, the KidGen Consortium has collected data on over 1,500 patients seen through the national MDT network.

The KidGen Consortium recently concluded the HIDDEN study, for which RPA Hospital was a lead site. This study investigated the utility of clinical whole genome sequencing (WGS) in patients with kidney failure of unknown cause. This world-first study had a diagnostic rate of 25% in a cohort of kidney failure patients who were undiagnosed after imaging, blood tests and kidney biopsy.

A wide variety of disease-causing variants were identified, including mitochondrial genome variants, highlighting some of the benefits of whole genome sequencing as a diagnostic tool.

Patients who were undiagnosed after the clinical-grade analysis performed in the HIDDEN study have been transitioned to an MRFF-funded study focused on undiagnosed families with suspected genetic kidney disease. This seamless transition from diagnostic to research analysis highlights another benefit of a WGS-first approach, which opens up avenues for further research genomic analysis or diagnostic laboratory re-analysis in undiagnosed patients. This advanced genomics study is currently actively recruiting and combines short-read WGS with long-read nanopore sequencing, RNA sequencing and organoid and animal modelling to find a diagnosis in undiagnosed kidney disease families.

Identifying a genetic diagnosis has immediate benefit in improving prognostic information and guiding family planning. Diagnosis also opens the ability to participate in current and future therapy trials. As for many other genetic conditions, there are limited current therapies available for those with genetic kidney disease. RPA Hospital is currently a study site for the IMPEDE-PKD study. This investigator-led clinical trial is studying metformin as a potential therapeutic for ADPKD.

District families with ADPKD are also being recruited to a genomic research study in collaboration with the Garvan Institute, focused on genetically undiagnosed ADPKD patients and on understanding the molecular basis of cyst development. The study utilises short and long-read genome sequencing, deep sequencing and single-cell RNA sequencing.

There are many exciting research opportunities within SLHD to improve care for families with genetic kidney disease, with many of the tools developed through this genomics research applicable to genetic disease across all systems.

Rare diseases

Whole exome sequencing at Concord Molecular Medicine Laboratory

29 February 2024 is Rare Disease Day – an opportunity to raise awareness and show support for the estimated 2 million Australians living with a rare disease. Around 80 percent of all rare diseases are genetic but can be complex to diagnose. Delays in obtaining accurate genomic diagnosis prevent early interventions and personalised care for patients.

Inherited neuromuscular disease is a prime example of how genetic testing is vital for management; especially as targeted therapies are being developed for specific genetic conditions. For example, the antisense oligonucleotide Tofersen was approved by FDA under the accelerated approval pathway in April 2023 for *SOD1*-amyotrophic lateral sclerosis.

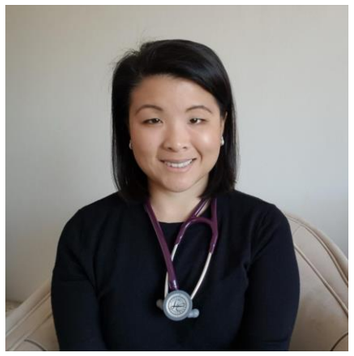
Medicare funded genetic testing for neuromuscular disease became available from late 2022. The Concord Molecular Medicine Laboratory has seen a significant uptake in referrals. The laboratory adopts a whole exome sequencing approach to allow for flexibility in the scope of analysis, and for future re-analysis as more gene disease associations are discovered. In 2023, the laboratory received a 7-fold increase in referrals for gene panels ranging from neuropathies, dystonia, ataxia and motor neurone disease. This has significant implications for resourcing and service delivery. Improvement in the efficiency of laboratory processes and workforce will be a major focus for the laboratory in 2024.

The diagnostic laboratory collaborates closely with the clinical and laboratory research groups led by Professor Steve Vucic and Professor Marina Kennerson, with the aim to create a seamless service from bedside to diagnostic and research. Patients and referring clinicians are encouraged to reach out to our group to look at unsolved cases.

Pictured: The Concord Molecular Medicine Lab team from left to right: Marion Stoll, Judith Wong, Khim Perkins, Kishore Kumar, Anthony Cheong, Michael Chin, Marina Kennerson, Danqing Zhu.

Our Stories

USA perspective of precision medicine in cardiology



Dr Michelle S Lim
Honorary Medical Officer, RPA Hospital

Dr Michelle Lim recently returned to Australia after completing a clinical fellowship at Washington University in St Louis, USA. Dr Lim is welcomed as a new member of the IPM&B's Strategic Advisory Council, a position which she will "job-share" with Dr Elizabeth Robertson, a long-standing supporter of the IPM&B.

Similar to other clinical streams, precision medicine is increasingly shaping the way that care is provided to patients with cardiac conditions. During a recent clinical fellowship at Washington University in St Louis, USA, I worked within a health system that enabled the expedient provision of personalised care to patients and families affected by heritable aortic diseases.

Aortic disease (aneurysm and dissection) is associated with significant morbidity and mortality. Patients with syndromal aortopathies (ie, Marfan Syndrome, Loeys Dietz Syndrome and Vascular Ehlers Danlos Syndrome) may manifest outward clinical features, but with significant overlap between the conditions. Patients with non-syndromal genetic aortopathies often do not exhibit specific clinical extra-aortic phenotypes, limiting the ability to distinguish between the genetically mediated conditions based on clinical features alone. There is significant variability in vascular risk profiles amongst these genetic aortopathies. As such, identifying the causative genetic variant has profound implications for clinical decision making, including but not limited to size thresholds at which prophylactic surgery is recommended, type of intervention undertaken (surgical vs endovascular procedures), as well as informing pregnancy and exercise recommendations.

Delivery of precision medicine in the USA is feasible and relatively straightforward and is the standard of care in daily clinical practise. Decision making to recommend diagnostic genetic testing for patients with aortic disease can be driven by cardiologist physicians. Whilst in real-world clinical practise, these undertakings are often carried out by cardiologists with expertise in aortopathy in large high-volume quaternary referral centres, genetic testing can be initiated by cardiologists throughout various medical settings (ie, smaller hospital and community clinics), reducing one of the potential barriers to accessing precision care.

In the USA, the cost of medical care is provided through various commercial and government supported medical insurance coverage types for the vast majority of patients. Despite considerable variability between insurance coverage types and between individual insurance policies, during my experience the high costs of genetic testing were often covered by medical insurance with a relatively small out-of-pocket cost to the patient.

Examination of a panel of heritable thoracic aortic disease genes is widely available through multiple genetic testing companies, many of which provide pre- and post-test counselling by telephone. The particular testing company utilised in our clinic sent buccal testing kits to patients via mail, which were then returned by patients in the mail, enabling testing to be easily undertaken by patients who live in rural parts of the country. Subsequently, the company usually provided test results with variant curation and a comprehensive report within 8 weeks of a buccal swab being submitted.

Health system structures in the USA and streamlined processes by which genetic testing for heritable aortic diseases may be undertaken, removes multiple potential barriers to accessing precision healthcare, enabling personalised medicine to be delivered widely and swiftly as the standard of care to all patients with heritable aortic conditions throughout the country, with profound implications for the management of and outcomes in patients and affected family members.

Innovations in oncology

The promise of liquid biopsy in precision medicine and cancer care

Dr Jenny Lee
Medical Oncologist, Chris O'Brien Lifehouse

Over the past decade, immune and targeted therapies have revolutionised the treatment of many cancer types. These drugs, and traditional chemotherapies, are no longer reserved for patients with inoperable advanced disease, but are increasingly used in the pre-operative (neoadjuvant) and post-operative (adjuvant) early-stage setting. However, risk stratification remains crude, outcomes are still poor, and many patients will re-present and die from their cancer.

Circulating biomarkers allow for the dynamic molecular and biological characterisation of all tumour metastases in real-time and are easily repeatable. For example, circulating tumour DNA (ctDNA) derived from patient tumours can be detected in blood, providing an opportunity to non-invasively detect and analyse tumour-derived mutations. Potential clinical applications of ctDNA include screening, detection of minimal residual disease and recurrence, identification of actionable and resistance mutations to guide treatment selection, predicting and monitoring of treatment response and prognostication.

Over the past few years, the Macquarie University and Melanoma Institute Australia liquid biopsy research program has made significant contributions towards the implementation of liquid biopsy in the routine management of melanoma patients. We showed that longitudinal ctDNA in melanoma patients receiving immunotherapy confirmed treatment response and resistance earlier and more accurately than standard CT imaging (Lee et al, Annals of Oncology). Importantly, we were able to accurately distinguish between pseudoprogression (initial increase in size of the cancer, likely due to inflammation, followed by tumour shrinkage – occurs in 5-10% of patients receiving IO) and true progression (Lee et al, JAMA Oncology).

The clinical utility of ctDNA was further expanded in our program to early-stage melanoma, where we showed that pre-operative ctDNA predicted melanoma specific survival and added value to the current AJCC staging system in resected stage III melanoma (Lee et al, Annals of Oncology). Citing this research, international experts even put forward the "futuristic concept of TNMB (B [liquid biopsy]) tumour classification" to open new horizons for precision medicine and adding to current standard of care to create better outcomes for cancer patients.

The Integrated Multimodal Precision Liquid Biopsy to Enhance MElanoma and NSCLC Treatment (IMPLEMENT) program, funded by the Medical Research Future Fund (CIA Rizos, $2.031 million) is a research collaboration between Macquarie University, Edith Cowan University, Melanoma Institute Australia, Chris O'Brien Lifehouse, Charles Gairdner Hospital and multiple industry partners. With a world-class research team including clinicians, internationally recognised researchers in liquid biopsy research, implementation scientists and health informatics scientists, this ambitious project's aim is to develop predictive and prognostic liquid biopsy signatures for clinical implementation in both early- and late-stage melanoma and NSCLC.

Programs such as IMPLEMENT will lead to exciting opportunities for Sydney Local Health District and Chris O'Brien Lifehouse, including rapid validation of novel predictive signatures and implementation of liquid biopsy into routine clinical care to transform the outcome of patients living with cancer.

Our Stories

Policy update

Australia redefines National Digital Health Strategy to focus on precision medicine

Federal, state and territory governments have set new priorities for digital health to align with the increasing demand for precision medicine. The updated National Digital Health Strategy 2023-2028 will assist the nation's health systems pivot towards personalised and preventative healthcare.

Australian Digital Health Agency CEO Ms Amanda Cattermole PSM said the Strategy and Delivery Roadmap were the result of a productive collaboration between federal, state and territory governments and shaped through extensive consultations with consumers, carers, healthcare providers, research organisations and technology innovators.

“In an age of precision medicine, characterised by healthcare innovations like wearable technology and AI driven genomic research, we are witnessing a paradigm shift towards personalised and preventative healthcare. The National Digital Health Strategy is essential to support this shift while fostering a connected, secure, inclusive and ethical healthcare system, backed by robust legislation,” Ms Cattermole said.

The strategy identifies four "change enablers" that will support the delivery of four targeted health system outcomes.

Change enablers

- Policy and regulatory settings that cultivate digital health adoption, use, and innovation
- Secure, fit-for-purpose, and connected digital solutions
- Digitally ready and enabled health and wellbeing workforce
- Informed, confident consumers and carers with strong digital health literacy.

Outcomes

- Digitally enabled: Health and wellbeing services are connected, safe, secure and sustainable
- Person-centred: Citizens are empowered to take care of their health and wellbeing, equipped with the right information and tools
- Inclusive: Citizens have equitable access to health services, anytime, anywhere
- Data-driven: Data is readily available and informs decision-making at the individual, community and national level.

The strategy also includes a roadmap which features the scope, approach, governance, key inputs, partners and priority actions to meet its vision.

The impact of multi omics on precision medicine

Professor Ron Trent
Director, IPM&B

The individual *omics* (genomics, transcriptomics, metabolomics, proteomics, epigenomics and many others) are well established approaches in research. Genomics and increasingly transcriptomics are routinely applied in clinical models of care, while metabolomics, proteomics and perhaps epigenomics, are starting to have an impact at the bedside as diagnostic markers. Starting to emerge in the medical context is *multi omics*, which describes the use of many omics to allow a more critical and in-depth assessment of cellular structure and function, with considerable interest presently in the cancer micro-environment.

Drivers for the roll out of multi-omics

- Impressive developments in analytic platforms enabling rapid and increasingly cheaper characterisation of multiple analytes (genes, mRNA species, metabolites and epigenetic markers). To date the technological focus has been on DNA gene sequencing.

However, equally important and increasingly sophisticated are the mass spectrometry-based methods for expanding the opportunities in proteomics and metabolomics (Dai X, Shen L. Advances and trends in omics technology development. Frontiers in Medicine 2022;9:911861).

- Single cell methodologies that allow the incredible diversity found within cell clusters to be examined at the single cell level. As sophistication in omics has increased, the focus has moved from “bulk” analysis (data generated from a number of cells collectively) to single cell testing which allows the myriad of differences between cells to be identified. Together with advanced sequencing technologies, the genome and transcriptome of a single cell can be characterised.

  It is predicted by Garvan researchers that oncology, immunology and haematology will be the first disciplines to benefit from the scRNA-seq and scDNA-seq approaches and examples are provided in their recent 2023 Nature Reviews Genetics paper. The same paper illustrates nicely the three steps for multi omics as (i) Tissue sample collection; (ii) Single cell sequencing and (iii) Bioinformatic analysis, which ideally should be conducted using a comprehensive single cell single LIMS (laboratory information management system) (Lim J, et al. Transitioning single-cell genomics into the clinic. Nature Reviews Genetics 2023;24:573-584 and Figure 1).

- The computational analytical power enabled by cloud computing, availability of knowledge-based databases and software tools. This armamentarium can now be expanded with sophisticated AI tools designed to analyse large and diverse data sets that require integration and interrogation against clinical information digitalised for accessibility. Societal and ethical considerations of AI in clinical practice are starting to be discussed but in the context of multi omics are made more challenging particularly in a discipline such as perinatology (Pammi M, et al. Multiomics, artificial intelligence, and precision medicine in perinatology. Pediatric Research 2023;93:308-315).

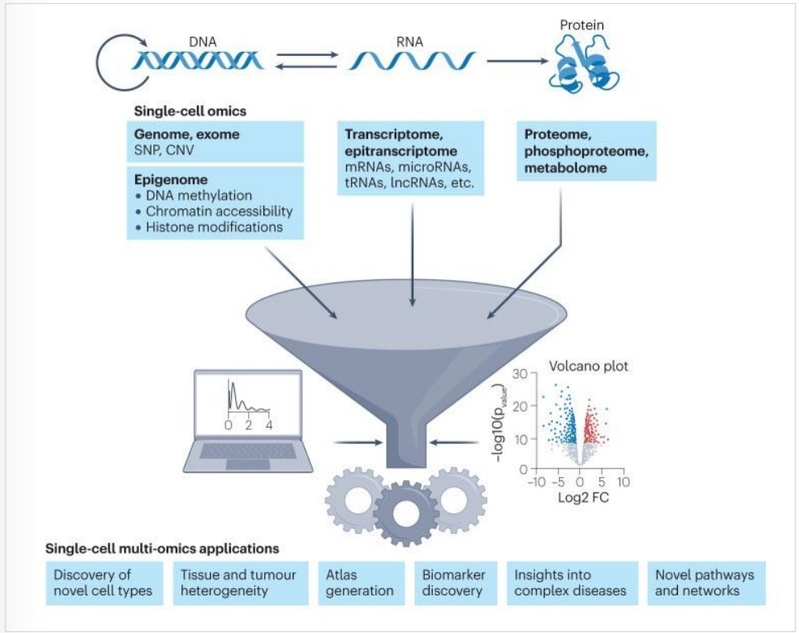


Figure 1. Baysoy A et al. Technological landscape and applications of single-cell multi-omics. Nature Reviews Molecular Cell Biology 2023;24:695-713.

Our Stories

Precision cancer model of care

Just as cancer research led the way in precision medicine, it is also harnessing multi omics to enable more sophisticated cancer sub-type classifications and predictions of their survival, new therapies and better monitoring for early and more effective treatment of relapse. Computational resources, including access to cancer dedicated databases and the addition of deep neural networks in AI, are all contributing to a better understanding of genomic instability, a hallmark of cancer, that goes on to promote genetic heterogeneity. Some of the findings from a multi omics approach in cancer are depicted in Figure 2.

IPM&B Annual Scientific Meeting 2024

To highlight the impact likely to be played by multi omics in precision medicine, the IPM&B's 2024 Annual Scientific Meeting will focus on multi omics as its central theme. The ASM will be held on Monday 14 October 2024, 1.30-4.30pm at the Kerry Packer Education Centre. Our keynote speaker is Professor Joseph Powell, Director of Translational Genomics at the Garvan Institute of Medical Research. More details, including the full conference program and registration link will be available soon. The ASM will be an in-person only event with opportunities for networking (70 places available).

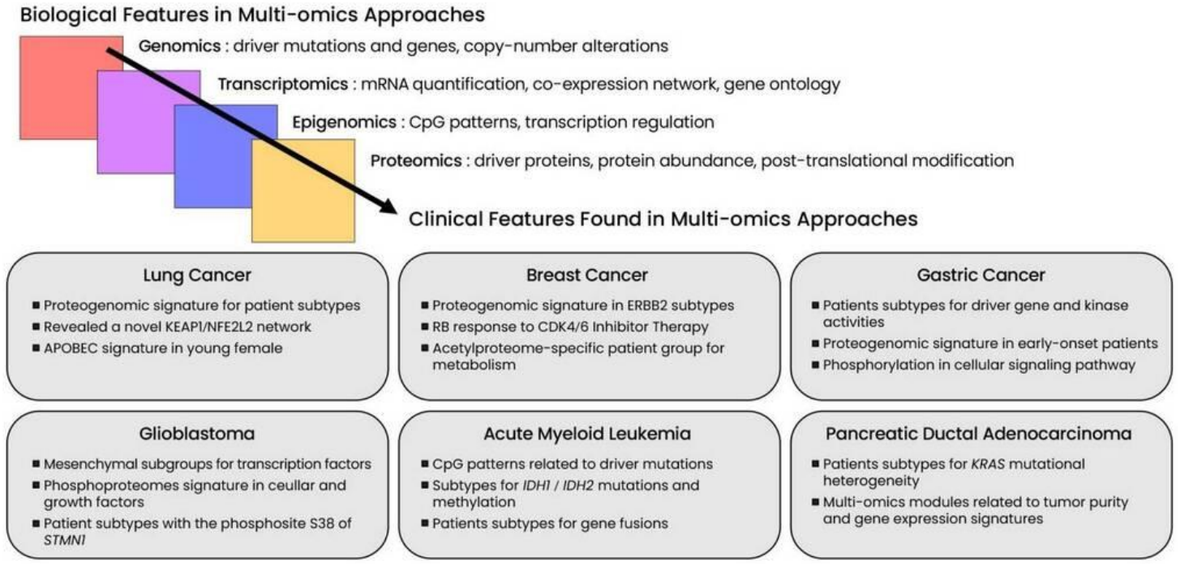


Figure 2. Heo YJ, et al. Integrative multi-omics approaches in cancer research: from biological networks to clinical subtypes. Molecules and Cells 2021; 44:433-443.

Profile

Introduction to the NSW Health Statewide Biobank

Professor Jennifer Byrne PhD
Director of Biobanking – NSW Health

A colleague once referred to biobanking as being like plumbing – sometimes hidden but always needed. Here I introduce the NSW Health Statewide Biobank as unique research infrastructure on the Sydney Local Health District campus that's designed to support biomedical research at scale.

My role is to serve as the Director of Biobanking – NSW Health. As such, the NSW Health Statewide Biobank falls within my responsibility, and I work at the Statewide Biobank on most days. However, the Statewide Biobank's origins predate my role by many years.

Around 10 years ago, there was a growing realisation that government could not financially support all health biobanks in NSW. Instead, a single biobank would be created that would differ from existing biobanks in several respects. As a statewide resource, it would be supported by several organisations – strategically overseen by the Office of Health and Medical Research, operated by NSW Health Pathology, and located in the Sydney Local Health District.

Rather than occupying existing laboratory space, the Statewide Biobank would be purpose-built within the Professor Marie Bashir Centre in Camperdown. This design allowed the Statewide Biobank to be built around process automation. As a result, the Statewide Biobank houses an automated BioStore -80°C freezer, with capacity to store ~3 million samples – one of only a handful of similar freezers in the country. Finally, instead of focusing on individual diseases or sample types, the Statewide Biobank would process and store samples from any human health condition.

The Statewide Biobank opened in 2017 and now supports ~30 research studies, doubling its sample cohort size over the past 2 years. The Statewide Biobank also supports the biobanking community, through educational seminars, and by developing protocols and biobanking apps that are freely shared. Given our experience in automation and biobanking at scale, the Statewide Biobank has much to offer other health biobanks. We are therefore supporting the planning of the new Sydney Biomedical Accelerator biobank. As local colleagues focusing on automated sample processing, we understand the challenges of delivering quality at scale.

All these achievements reflect our talented and committed team, led by Candace Carter as Operations Manager, Dr Beth Caruana as Senior Scientist, and Dr Michael Evtushenko as Client Services Manager.

Our Stories

Precision oncology

Professor Ron Trent
Director, IPM&B

The era of precision oncology has progressed further to comprehensive gene profiling with the important announcement of OMICO's Cancer Screening Program led by Professor David Thomas from UNSW. Professor Bing Yu and the Somatic Cancer Testing team at RPA Hospital have been invited to contribute to the OMICO study by providing NATA-accredited somatic cell DNA testing reports.

Bing and colleagues have recently published a review on comprehensive gene profiling, emphasising the challenges that arise as more genes are analysed in tumor tissue. The increased number of studied genes raises the likelihood of identifying inherited (germline) cancer genes, which could have broader implications for both the patient and their genetic relatives (see Al-Shinnag M, Cheong PL, Goodwin A, Trent R, Yu B. Germline potential should not be overlooked for cancer variants identified in tumour-only somatic mutation testing. Pathology 2024;56(4):468-72).

As advanced genomic testing evolves, the role of AI in healthcare becomes increasingly significant. With large data sets becoming more challenging to process and interpret, there is a growing need to explore how AI can support complex models of care, involving laboratories, clinicians, patients, and families.

Free genomic testing: rare, incurable & advanced cancers

OMICO Cancer Screening Program

OMICO is an independent, not-for-profit company with a core focus on precision oncology. OMICO's Cancer Screening Program (CaSP) is providing free comprehensive genomic profiling (CGP) to 23,000 Australians with advanced or incurable cancers and identifying potential matches for patients to clinical trials with new targeted therapies. This is the largest cancer genomics initiative in Australia.

CaSP has three parts

Part 1: Screening 23,000 patients with advanced, incurable or poor prognosis cancers

Screening of up to 23,000 patients who have advanced, incurable or an earlier diagnosis of a poor prognosis cancer using CGP at no cost to the patient. Genomic profiling is used to analyse the molecular characteristics of a patient's tumour and gather genetic and clinical information to help identify specific characteristics about the tumour. The genomic profiling is carried out by NATA accredited pathology laboratories.

A team of experts reviews the genomic profile of the tumour with other clinical and patient information. A Molecular Oncology Board (MOB) Report provides the genomic profiling pathology report to the referring clinician, as well as potential treatments and trials for patients.

Once a patient has provided written consent to participate in CaSP, it typically takes 8-10 weeks for the referring clinician to receive the MOB report. Patients indicated as urgent by the referring clinician will be fast-tracked, with MOB reports returned in 5-6 weeks.

Part 2: An observational cohort study of people enrolled in CaSP

CaSP does not deliver any specific intervention and is not a clinical trial. Its primary purpose is to make CGP more broadly available to people with an unmet need, and to use that information to link people to potential clinical trials. It is important that the information collected by CaSP be used to guide how CGP is implemented in Australia and to evaluate what use it provides to the community.

Part 3: Research Registry and Biobank

CaSP will establish a research registry and bioresource to facilitate the observational cohort study and provide a resource for future use, including clinical trial and treatment matching, and epidemiological and public health research studies to facilitate ongoing research into cancer and its treatment.

Who can participate in CaSP?

- Patients aged 16 years and older with an advanced, incurable or an earlier diagnosis of a poor prognosis cancer who are willing and fit enough to participate in a clinical trial are eligible.
- Patients can be referred to CaSP early in their cancer journey. That is, after initial diagnosis of pathologically confirmed *incurable, advanced and/or metastatic cancer of any histological type* or an *earlier diagnosis of a poor prognosis tumour.*
- Eligibility for CaSP does not require patients to have failed Standard of Care treatment.

Not all comprehensive genomic profiling leads to a patient match with a clinical trial.

What does participation involve?

- Agreeing to all parts of CaSP
- Consenting to the access of samples held by pathology centres to perform CGP
- Consenting to the access to your health records
- Evaluation of molecular and clinical information for trial matching or molecular guided treatment
- Donating blood samples and other tissues
- Completing questionnaires
- Consent for access for Medicare / PBS data.

Artificial intelligence in healthcare

New AHPRA Guidelines

The Australian Health Practitioner Regulation Agency (AHPRA) has released essential principles for health practitioners to follow to ensure they meet their professional obligations when using AI in practice.

Accountability

Regardless of the technology used in healthcare, practitioners are responsible for delivering safe and quality care and must adhere to their Code of Conduct. They must apply human judgement to AI outputs and ensure any AI tools are fit-for-purpose before use. TGA approval does not relieve practitioners from their responsibility to oversee and verify AI tools. For AI scribing tools, practitioners must check the accuracy and relevance of generated records.

Understanding

Health practitioners must thoroughly understand the AI tools they use to ensure safe and professional practice. They should review the product information, including the tool's training and testing processes, intended use, limitations, and unsuitable clinical contexts. Knowing the AI tool's intended use will assist practitioners assess its appropriateness and associated risks, such as diagnostic accuracy, data privacy, and ethical issues.

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Additionally, practitioners should be aware of how data is used for retraining the AI, its storage location, and handling.

Transparency

Health practitioners should inform patients about their use of AI and address any concerns. The level of detail provided should match the AI's role: minimal technical details are needed if AI aids diagnostic image interpretation, but more information is required if AI records consultations, particularly regarding how it handles personal data. For AI tools that could affect patient privacy, such as public generative AI software, practitioners must explain the implications for data collection and use.

Informed consent

Health practitioners must involve patients in decisions about using AI tools that require their personal data, such as diagnostic devices or AI scribing tools. Obtain informed consent from patients, ideally documenting their response in the health record. This is crucial for AI models that record private conversations, as failure to obtain consent could have legal implications. AI transcription software should include an explicit consent step before recording begins.

Ethical and legal issues

Relevant professional obligations for using AI in healthcare include:

- *Confidentiality and privacy*: Ensure patient data is handled in compliance with privacy laws, checking that AI training data doesn't breach confidentiality.
- *Bias*: Be aware of and address biases in AI algorithms to ensure the health and safety of all patients, including Aboriginal and Torres Strait Islander people and those from diverse backgrounds.
- *Legal compliance*: Follow all applicable laws and regulations related to AI use, including those from the TGA and local governments.
- *Governance*: Understand and adhere to your employer's governance procedures for AI implementation, use, and monitoring.
- *Professional indemnity insurance*: Verify that your professional indemnity insurance covers the use of AI tools in your practice and consult your provider if needed.

RCPA announcement

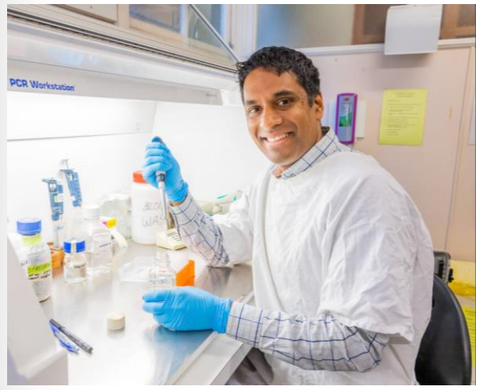
Key recommendations to improve accessibility to PGx testing

On International Pathology Day, the Royal College of Pathologists of Australasia (RCPA) called for urgent action to improve access to pharmacogenomic (PGx) testing across Australia. With increasing demand for PGx testing, the RCPA has outlined several key recommendations:

- expanding public funding through the Medicare Benefits Schedule
- enhancing education for both clinicians and patients on the benefits of pharmacogenomic testing
- investing in research to better understand genetic variation across Australia's diverse population, including First Nations people.

Additionally, a new trial aims to further demonstrate the benefits of pharmacogenomic screening in Australian cancer patients.

Clinical champions



Associate Professor Kishore Raj Kumar

Associate Professor Kishore Kumar is a neurologist at Concord Hospital. He completed his PhD on the genetics of movement disorders in 2014 under the supervision of Professor Carolyn Sue. During his PhD, he undertook an overseas elective at the Institute of Neurogenetics, University of Luebeck, in Germany, under the mentorship of Professor Christine Klein. This was a unique experience working in an international laboratory while experiencing life in a small German town. He followed his PhD studies with a NHMRC Early Career Fellowship at the Garvan Institute under the supervision of Professor Marcel Dinger and Associate Professor Mark Cowley.

He moved from the Royal North Shore Hospital to Concord Repatriation General Hospital in 2019. At Concord Hospital, he has been working at the Neurology Department and Neuromuscular Clinic. He works in the Hereditary Neuropathy Clinic (linked with Professor Marina Kennerson's lab at the ANZAC Institute). He also works with the team at the Molecular Medicine Laboratory (and Genetic Pathologist, Dr Anthony Cheong) to identify a genetic diagnosis for his patients.

Additionally, he is a visiting neurologist at the Neurogenomics Clinic at St Vincent's Hospital with Associate Professor Kathy Wu. His clinical work is integrated with neurogenomics research at the Garvan Institute. At the Garvan, he heads the Translational Neurogenomics Group within the Genomics and Inherited Disease Program and is a Conjoint Associate Professor with UNSW.

Through his work at the Garvan Institute, Associate Professor Kumar led major studies using short read genome sequencing (srGS) to investigate neurogenetic disorders such as dystonia, ataxia, hereditary spastic paraplegia, and mitochondrial disease.

His work on srGS for mitochondrial disease with Dr Ryan Davis, Professor Sue and Associate Professor Cowley led to the successful application to make genome sequencing for mitochondrial disease a Medicare rebatable test. This improved access for genetic testing for mitochondrial disease across Australia.

Associate Professor Kumar also created the world's first genome database for dystonia. His recent work with visiting clinician-scientist Dr Avi Fellner showed that reanalysis of this database can improve the diagnostic yield from 11.7% to 18.9%. He also used the database for the discovery of major new dystonia genetics such as *AOPEP* and VPS16, transforming our understanding of the genetics of dystonia.

He now leads several major neurogenetics research programs. This includes being a Co-Lead for the Monogenic Network, Global Parkinson's Genetics Program (GP2). Leveraging off this study, he is the lead investigator for the MRRF Funded ($2.95M) Monogenic Parkinson's disease Australia (MonoPDAus) initiative, undertaking srGS in 1000 patients and family members with early onset or familial Parkinson's disease. Furthermore, he is the lead for Ainsworth 4 Dystonia Research Mission, trying to uncover the genetic basis of dystonia using long read sequencing and RNA sequencing.

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His recent work with bioinformatician Dr Ira Deveson has focused on using long read sequencing to simplify and improve the diagnosis of cerebellar ataxia and genetic muscle disorders.

Associate Professor Kumar is primary supervisor for two PhD students, neurologists Dr Dennis Yeow and Dr Laura Rudaks. Moreover, he co-supervises a PhD student Victor Flores-Ocampo at QIMR with Associate Professor Miguel Renteria. Recently, his student Dr Sue-Faye Siow completed her PhD into biomarkers for hereditary spastic paraplegia.

Associate Professor Kumar has had many awards of his career including the Leonard Cox Award for contribution to neuroscience (2016). His goal is to use advances in genomics to improve the diagnosis of his patients, and to translate these benefits into improvements in clinical care using a personalised medicine approach.

Highlights from recent events

IPM&B 2024 ASM: Unlocking disease mechanisms through multi omics approaches

The IPM&B's 2024 Annual Scientific Meeting held on 14 October featured an exciting lineup of speakers who explored cutting-edge advancements in multi omics research.

The keynote address by Professor Joseph Powell, titled *Single Cell Genomics in the Clinic*, highlighted the transformative potential of single-cell technologies in clinical applications, offering new insights into disease mechanisms at an unprecedented level of resolution.

Pictured: Professor Joseph Powell.

Professor Anthony Linton gave a presentation on the use of multi omics approaches to understand dust-related diseases, shedding light on how integrating genomics, proteomics, and other omics technologies can unveil complex environmental health interactions.

Professor Marina Kennerson discussed how the 3D organisation of the genome can reveal novel genetic insights and disease mechanisms.

Finally, Associate Professor Albert Lee emphasised how proteomics is key to understanding the molecular underpinnings of disease and its potential for therapeutic development. The event showcased the power of multi omics in advancing our understanding of biology and medicine.

Pictured: Professor Anthony Linton.

Precision Medicine Consumer Group

2024 meeting program – key highlights

The 2024 meeting program of the Precision Medicine Consumer Group brought together experts, researchers, and consumers to discuss the latest advancements in precision medicine, including pharmacogenomics, oncology, and familial hypercholesterolaemia. Here's a summary of the key discussions and outcomes from the series of virtual and in-person meetings:

- **Pharmacogenomics (PGx)**: The program kicked off with an update on Professor Tim Lambert's research into pharmacogenomics and mental health. The session also focused on the implementation of PGx into clinical care at RPA Hospital, specifically in oncology, cardiovascular care, and metabolomics. This meeting highlighted the growing potential of PGx in personalising treatments and improving patient outcomes.
- **Precision Oncology**: Professor Bing Yu led an engaging session on the advancements in somatic cancer DNA testing at RPA Hospital. The discussion centered around the PrOSPeCT program, Australia's largest cancer genomics initiative, which aims to revolutionise cancer care by using genetic insights to inform treatment strategies. The meeting underscored the importance of precision oncology in offering targeted therapies based on genetic markers.
- **Familial Hypercholesterolaemia (FH)**: Professor David Sullivan presented a grant-funded project focused on improving the understanding of Cascade screening for FH among primary healthcare providers. Consumer feedback was sought regarding the FH Lifelong Management App, designed to support individuals managing FH throughout their lives. The session also highlighted the work of FH Australia, a charitable foundation advocating for families affected by this genetic condition.
- **2024 Wrap-Up**: The final meeting of the year took place in person at RPA Hospital, where attendees were updated on the implementation of PGx testing at the hospital. A Consumer Rep roster for the PGx Expert Recommendation Panel was introduced, and feedback was gathered on PGx Reporting formats. The session concluded with a thank-you morning tea, celebrating the contributions of all those involved in these important initiatives.

Throughout the year, the meetings fostered collaboration between precision medicine experts and consumers, and we look forward to continuing these discussions and seeing further progress in 2025.

Pictured: members of the Precision Medicine Consumer Group.

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