KCCG NEWS ISSUE 5

Enabling precision health

The KCCG team and whole genome sequencing laboratory

In its new iteration, the Kinghorn Centre for Clinical Genomics is focused on realising the clinical value of the genome. With the launch of Genome.One, the first of KCCG's missions was achieved in the context of rare and inherited disease diagnosis. This launch also resulted in a transition of all clinical, production and directly commercialisable activities into Genome.One.

With the major shift in focus for KCCG, in parallel with rapid developments across the clinical genomics landscape, we have redefined KCCG's mission in line with the advances in clinical genomics and the current healthcare, research and political environment.

In its next phase, KCCG will focus on the following areas: identifying new medically-significant genetic variants by mining population-scale genomic data and associated health records; expanding the clinical utility of whole genome sequencing particularly searching for disease-related variants in noncoding regions of the genome; accessing, implementing and evaluating the most advanced and efficient genomic technologies; establishing genomic tests for cancer diagnosis, prognosis, and risk prediction; and developing targeted educational programs and resources for health professionals, patients and communities.

We are already working on projects that integrate the skills and knowledge of team members across all programs to ensure that we are not siloed and make the most of our diverse expertise.

Major project updates

Medical Genome Reference Bank

The Medical Genome Reference Bank (MGRB) has already met its goal of sequencing 75% of the participating cohorts in 2017. This brings the total number of genomes accessible through the MGRB Data Portal to just under 3000.

The MGRB Program is sequencing and analysing the genomes from healthy, older people to create a high quality database relatively free of damaging genetic variants. It is one of three major projects within the $24 million Sydney Genomics Collaborative.

The MGRB Data Portal is already helping researchers worldwide determine whether variants found in their own studies are associated with disease. More than 100 researchers have begun exploring summary information, and others have applied to access the wealth of deeper genomic and phenomic data it contains.

Genome Power

Garvan recently launched 'Genome Power', the Lions Kids Cancer Genome Project funded by the Lions Clubs International Foundation and the Australian Lions Childhood Cancer Research Foundation, to harness the power of the genome to radically transform the understanding and treatment of kids cancer.

Genome Power will be supporting Australia's national personalised medicine program for childhood cancer - Zero Childhood Cancer Program, led by Children's Cancer Institute in partnership with the Kids Cancer Centre, Sydney Children's Hospital, Randwick.

In its first three years, Genome Power will provide whole genome sequencing and analysis for 400 children with high-risk cancer across Australia. Genomic information from tumour DNA will assist clinicians in identifying the best treatment strategies for these children. In addition, sequencing of germ-line DNA (from blood) is being undertaken to identify variants that predispose children to cancer.

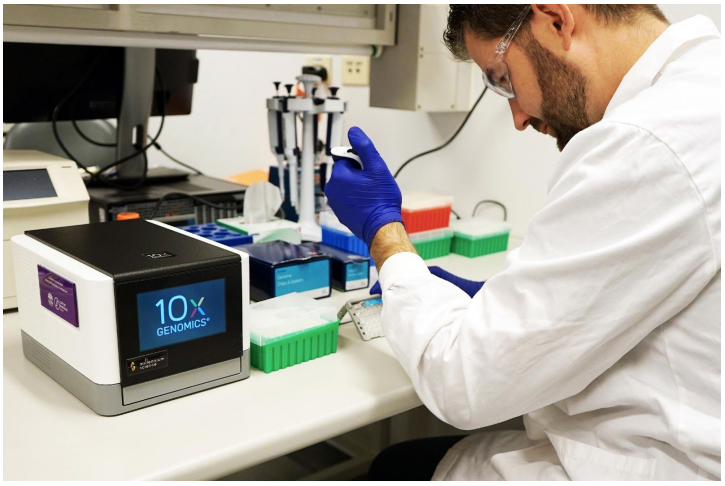
In the pilot phase, genomes have been sequenced and analysed from over 35 children with high-risk cancers in Sydney, including tumours of the central nervous system, leukemias, neuroblastoma, and sarcoma. KCCG researchers Drs Mark Cowley and Marie Wong have analysed the tumour genomes, focusing on automating variant analysis. Dr Mark Pinese, in the Cancer Genome Medicine Laboratory led by Prof David Thomas, has undertaken the analysis of over 22 germ-line genomic sequences.

Curation is done collaboratively with the Zero Childhood Cancer curation team. They take their findings to the Zero Childhood Cancer Multidisciplinary Tumour Board for discussion and recommendations to clinicians in a clinically useful timeframe.

The pilot is already demonstrating the value of information from whole genome sequencing to improving patient management. The national rollout of the Zero Childhood Cancer Program aims to commence in the next month, and around 100 children with high-risk cancer from across Australia are expected to be enrolled over the coming year.

Technology updates

Chromium Genome Solution



KCCG has acquired the Chromium Genome Solution from 10x Genomics Inc, thanks to a $220,000 Research Equipment Grant from the Cancer Institute NSW.

This new technology helps researchers at KCCG, Garvan and across NSW to better detect and interpret large, complex structural rearrangements of DNA.

The Chromium does this by using a 'barcode' strategy to mimic a long read approach on short read sequencing technologies, which ensures a high quality at a relatively low cost.

Short read technologies require the DNA to be broken into small fragments for sequencing. When this is done using the Chromium, fragments from the same regions are labelled with the same molecular barcode. This makes it easier to assemble and align the genomic sequence correctly and thus detect structural rearrangements.

Dominik Kaczorowski, KCCG Senior Laboratory Scientist, prepares samples to be used in the Chromium.

Staff profile

Dr Marie-Jo Brion, Scientific Officer

Dr Marie-Jo Brion brings a background in highly collaborative population health research to her role as scientific officer at KCCG. Originally from Perth, Dr Brion obtained her PhD in epidemiology in Bristol followed by fellowships at the Broad Institute and the University of Queensland.

While epidemiology was her initial interest, Dr Brion was increasingly struck by the impact genomic data was having in population health research, and a fellowship at the Broad Institute "cemented her passion for genomics."

Taking on the role of scientific officer at KCCG was a logical next step for Dr Brion, who wanted to use her experience in research and collaboration to help others deliver research programs.

“I wanted to continue to be involved in research, and help drive exciting new projects in the genomics space, by engaging and interacting with different people.”

It was the strong focus on translational research that most attracted Dr Brion to KCCG.

“It is a big challenge, getting scientific research to translate with impact, but KCCG is involved in front-line translation – taking brand new technologies straight to the clinic, which I think is one of our major strengths.”

Dr Brion now helps run some of KCCG’s key research programs and data resources, including the Medical Genome Reference Bank in collaboration with the Sax Institute and Monash University. One aspect of her role, that she has found particularly exciting, is working with the executive team to develop the 4-year strategy for the next stage of KCCG.

“It’s great to come in when KCCG is starting to enter a new phase,” Dr Brion says, “to be involved in discussions about how to take our research to the next level, it’s a really exciting time to be working here.”

Grants and awards

The KCCG Phenomics Team in partnership with OHSU, Berkeley Labs, JAX, University of Pittsburgh, and Queen Mary University of London were awarded an NIH grant of USD $250,000 to support their contributions to the Monarch Initiative, a global project to apply computational reasoning to phenotype comparison within and across species.

Publications and conferences

Publications

Researchers at KCCG contributed bioinformatics expertise to a collaborative *Nature* paper on 15 February entitled Whole-genome landscape of pancreatic neuroendocrine tumours.

A study on using whole exome sequencing to diagnose Mendelian disorders at Sydney Children’s Hospital and the KCCG led to a paper Gonadal mosaicism of a novel IQSEC2 variant causing female limited intellectual disability and epilepsy published 15 March in the European Journal of Human Genetics with authors Dr Lisa Ewans, Dr Mark Cowley and A/Prof Marcel Dinger.

KCCG researchers, along with researchers at the Garvan Institute, St Vincent’s Hospital, the University of Sydney and the University of New South Wales, published a paper on non-coding regions of the genome associated with cancer, entitledCancer-associated noncoding mutations affect RNA

G-quadruplex-mediated regulation of gene expression on 15 March in Nature Scientific Reports with authors including Dr Mark Cowley and A/Prof Marcel Dinger.

KCCG researchers were part of another study with Garvan and St Vincent's, on using next generation sequencing to identify germline variants in patients with pituitary adenomas. A paper on their findings, Germline variants in familial pituitary tumour syndrome genes are common in young patients and families with additional endocrine tumours, was published 20 February in the European Journal of Endocrinology with authors including Dr Mark McCabe, Dr Velimir Gayevski, Dr Mark Cowley and A/Prof Marcel Dinger.

Conferences

KCCG exhibited at the *38th Annual Lorne Genome Conference* in Victoria (12-14 February). This conference showcased research on the organisation and structure of the genome and featured prominent research leaders from USA, China and South Korea. Dr Cowley was an invited panel member of a lunchtime panel on bioinformatics, and A/Prof Dinger was on the organising committee.

Dr Cowley also attended the *Deciphering Genome Big Data Symposium* in Tokyo on 21 March, as an invited plenary speaker, talking on deciphering whole genome sequencing data at scale and in the clinic for rare disease and cancer diagnosis.

A/Prof Marcel Dinger led a data-focused workshop at a *National [Genomics] Initiatives: Opportunities for Knowledge Exchange and Collaboration* meeting in London on 24 May. A/Prof Dinger also presented on genomics in healthcare at the *12thInternational Workshop on Advanced Genomics* in Tokyo on 29 June.

Dr Simon Kocbek attended the *30th IEEE International Symposium on Computer-Based Medical Systems* in Thessaloniki, Greece (22-24 June). Dr Kocbek and Dr Tudor Groza had a poster presentation with a full paper accepted on how to improve methods for extracting disease-phenotype relations from text, such as scientific literature, to help with research and clinical diagnosis.

In the media

Late last year, we shared the inspirational story of eight-year-old Alan, whose life-threatening immune disorder has been held at bay through the power of genomic information. You can explore more about his journey, his family's dedication, and the interdisciplinary team who helped change his life here.

An update to Alan's story was featured in ABC's Ask the Doctor series, in the episode on genes and genome sequencing aired on 4 July. This episode also included interviews with A/Prof Marcel Dinger and Ms Mary-Anne Young (Genetic Counsellor, Genome.One) in a segment exploring the host's experience of having their genome sequenced and results returned.

A/Prof Dinger, Alan, and Ms Young filming for the ABC's Ask the Doctor series.

Other coverage included the April edition of the *Australian Women's Weekly* featuring an article about the Williams family. Their daughters, Jaeli and Dali, have a rare variation in the SYNGAP1 gene which causes seizures and other serious neurological conditions. After many years of searching, they were diagnosed by whole genome sequencing at the KCCG. The article tells the Williams' story of living with a rare disease, the impact of a diagnosis, and the importance of medical research.

A/Prof Marcel Dinger was interviewed on *ABC News at Noon* about the Medical Genome Reference Bank launch. The story was covered widely, with stories in the *Courier Mail*, *Daily Telegraph*, *Herald Sun*, *GenomeWeb*, the *PHG Foundation*. We were also featured in a case study for the National Computational Infrastructure.

Events

Minister Skinner launching the MGRB at the second Sydney Genomics Collaborative Scientific Symposium, Dr Gayevskiy presenting at the Clinical Data Analysis course in Hong Kong.

Showcases

We hosted our fourth showcase on 3 April. A/Prof Marcel Dinger presented on the vision for KCCG in enabling precision healthcare, Dr Andrew Stone on the translation of KCCG's cohort research into Genome.One, Dr Mark Cowley on

personalised medicine and cancer genomics, and Bronwyn Terrill on educating professionals and empowering communities.

Our fifth showcase, held on 6 July, consisted of an hour of presentations from Genome.One's genetic specialists and scientists on realising precision health by transforming counselling, laboratory and pathology practice. Speakers included A/Prof Marcel Dinger on the vision for KCCG and Genome.One to transform clinical practice and medical research, and three Genome.One team members: Dr Ben Lundie on frontiers in genomic laboratory practice, Prof Leslie Burnett on moving from from diagnostic to precision medicine, and Ms Mary-Anne Young on consent in the genomics era.

Clinical Genomic Data Analysis course

KCCG and Genome.One ran a Clinical Genomic Data Analysis (CGDA) course for the Hong Kong Hospital Authority from 7-10 March. The course gave participants a practical understanding of how clinical genomic data is produced and interpreted, to support the implementation of genomics in their practice.

Over 100 people attended each lecture, including pathologists, haematologists, clinical scientists and paediatricians, and over 50 people registered interest for the 16 workshop places.

Post-workshop evaluations were positive, with participants commenting that the course was "very informative and practical" and left them better equipped to implement clinical genomics, including being "really helpful for data analysis and interpretation and genetic report writing."

Visits and seminars

KCCG/Garvan hosted a seminar, "Deciphering the Genome using Community Driven Approaches" on 23 February, by Dr Heidi Rehm, Chief Laboratory Director at the Partners Laboratory for Molecular Medicine, the Clinical Director of the Broad Institute Clinical Research Sequencing Platform and Associate Professor of Pathology at Brigham & Women's Hospital and Harvard Medical School. Following the seminar, Dr Rehm met key members of the Australian Genomics Health Alliance (AGHA) to discuss best practices in sharing variants between laboratories.

Sir John Chisholm, Executive Chairman of Genomics England, visited the Garvan to provide his thoughts, both face-to-face and in a four part series of interviews on the Genomics England 100,000 genome project and the development of genomic research and applications for the future.

Sydney Genomics Collaborative Scientific Symposium

KCCG hosted the second Sydney Genomics Collaborative Scientific Symposium on 16 December 2016. Attendees heard updates on the Collaborative's programs, with a particular focus on cohorts, including the launch of the Medical Genome Reference Bank (MGRB) by the Minister for Health, Jillian Skinner.

Welcoming new team members

KCCG continues to expand with the recruitment of a number of new staff members; Dr John Grady, Senior Research Officer for Cancer Genomics, Dr Alexander Drew,

Senior Research Officer for Clinical Genome Informatics, Ahmed Muaz, Principle Software Engineer for Clinical Genome Informatics, Andrew Gibb, Science Writer/Content Producer for Education and Communication, and Dr Marie-Jo Brion, Scientific Officer for KCCG.

Mr Peter Priestley (Hartwig Foundation Australia), Dr Elizabeth Palmer (Sydney Children's Hospital Network), and Dr Ryan Davis (Kolling Institute) joined KCCG as visiting scientists.

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