KCCG NEWS ISSUE 6

Welcome to the sixth edition of KCCG News. In the last couple of months we have focused on how to leverage our unique interdisciplinary expertise to tackle some of the most persisting challenges in clinical genomics.

To make a forceful impression on one of these challenges, making clinical use of more of the genome, we held our first hackathon on mining the non-protein-coding genome. This was an exciting experiment in getting our team with divergent expertise to work together on a common grand challenge in a very different way.

Since our last newsletter, we have also contributed to major launches of genomics programs, collaborated on national conversations about genomics and developed valuable new resources for the national genomics community.

Marcel Dinger, Head of KCCG

Health Hack

The KCCG team during our first hackathon

KCCG ran its first Health Hack on 16-18 August. This brought together more than 20 staff members from our six programs for a 48-hour blitz to improve our analysis and interpretation of the non-protein-coding genome.

We focused on the non-protein-coding regions because we know very little about them, even though they comprise over 98% of the human genome. Improving our understanding of these regions has huge potential to unlock diagnoses for patients with rare conditions as well as common, complex ones.

While some of the non-protein-coding regions are barely understood, others have important roles in enhancing, blocking and fine-tuning what genes are expressed in different parts of our body or different times during our development. Our genome even includes non-human DNA, which could have a role in cancer.

80 coffees, 15 pizzas, 12 thai dinners and 5 tubs of gelato later, our 8 teams and a few dedicated night-owls developed:

Databases for non protein-coding regions of likely medical relevance.

Bioinformatics methods to identify rare genetic variants, clinical impact of non-coding genes and non-human DNA as alternative causes of undiagnosed conditions.

Visualisations for genomic data using Apache Superset, an off-the-shelf business analytic tool.

Resources to promote others' understanding of the non-protein-coding genome.

Our Translational Genome Informatics team will be refining these new tools and resources so that they can be applied to undiagnosed individual's cases. This highly collaborative effort put into practice our vision of connecting our different disciplines to achieve the best possible translational outcomes and has laid the intellectual and practical foundations for future work in this challenging domain.

Major project updates

Garvan-Weizmann Centre for Cellular Genomics

Rina Michael, Executive Director of Weizmann Australia, and Dr Kate Patterson, Garvan Visual Science Communicator, experiment with VR at the Garvan-Weizmann Centre for Cellular Genomics launch.

The Garvan-Weizmann Centre for Cellular Genomics was officially opened on 3 August as the only multidisciplinary centre for cellular genomics in Australia. KCCG is now housed in this collaborative space, opening up amazing opportunities for advancing our work.

Cellular genomics is the study of the genetic makeup of thousands of individual cells at a time. Because it uncovers information about each individual cell, instead of averaging information from a large group, cellular genomics has the potential to revolutionise our understanding of many diseases and develop personalised medicine approaches.

A number of KCCG's teams have already begun collaborating with the centre, including the Genomic Technologies group who will soon offer access to new sequencing platforms in partnership with Garvan-Weizmann.

KCCG staff have also received Garvan-Weizmann grants. A/Prof Marcel Dinger, Head of KCCG, and Bronwyn Terrill, Education and Communication Program leader, were awarded a grant to research teacher roles in learning genomics concepts with molecular animations. This is in partnership with Dr Kate Patterson, Garvan Visual Science Communicator and educational researchers at the Weizmann Institute of Science.

Dr Martin Smith, Genomic Technologies Program leader, together with Dr Igor Ulitsky from the Weizmann Institute of Science and Prof John Mattick, Garvan Director, were awarded a Garvan-Weizmann collaborative grant to investigate noncoding RNA activation during cell regeneration.

Official launch of the Genomic Cancer Medicine Program

The Genomic Cancer Medicine Program, led by Kinghorn Cancer Centre Director Professor David Thomas, uses genomic information to improve the understanding, early detection, and management of cancer through two programs: Molecular Screening and Therapeutics Program (MoST) and Genetic Cancer Risk in the Young Study.

The Genetic Cancer Risk in the Young Study is now open at The Kinghorn Cancer Centre. It has been formed to investigate the inherited causes of cancer, by recruiting young people with cancer and their relatives. There are currently 272 participants enrolled; 203 cancer patients and 69 family members. The study will be using whole genome sequencing to identify variants in all 20,000 genes. The aim of obtaining this large amount of genetic information is to identify those at increased cancer risk, allowing clinical risk management including personalised surveillance and treatment options to be put in place and more fully informing life decisions.

A further 311 patients are enrolled in the MoST Program, which focuses research on rare and neglected cancers. The patients enrolled in the program have advanced cancer and no further standard treatment options. Medical oncologists, scientists and bioinformaticians are working together to screen patients, whilst they are receiving their last line of standard therapy.

Dr Mark Cowley, Tumour Genomics Program leader, and Dr John Grady, Senior Research Officer, are performing the analysis and genomic interpretation of the MoST tumour samples. They look at a suite of ~400 cancer genes, many of which

can already be matched to a potential treatment, or are likely to have a targeted treatment in the future.

The team have also been working hard to automate and simplify large parts of this process, so the MoST Program can get answers back to treating clinicians as quickly as possible.

“We’ve automated the pipeline from start to finish, including identifying actionable variants and matching with potential treatments,” said Dr Grady.

If the molecular screening identifies a biomarker, clinicians use this information to guide therapy for patients. Of the 197 patients that have had molecular screening results returned, 76 patients have been enrolled onto clinical trials at The Kinghorn Cancer Centre.

“Studying rare cancers is a prime opportunity for precision cancer medicine,” said Dr Cowley, “We are able to recommend good, targeted treatments from well-studied cancers to patients with the same variants, and benefit a whole set of underserved cancers”.

Technology updates

3D Printing

KCCG staff have been partnering with the Garvan-Weizmann Centre for Cellular Genomics to bring innovative ideas to life through 3D printing.

The centre has tools for prototyping and construction, including a 3D printer, alongside its state-of-the-art technologies for cell handling, genomics and informatics.

Hira Saeed and Wenyan Li, both cytometrists in the Garvan-Weizmann Centre, have been working with Garvan staff and collaborators to create 3D printed equipment and biological models. These can be novel ideas, or modified versions of existing items to better suit staff’s needs.

"We are constantly thinking of ways to optimise the solutions we provide for researchers and collaborators, having the 3D printer allows us to think outside the box,” said Ms Saeed.

James Ferguson, Genomic Systems Analyst in our Genomic Technologies Group, worked with them on a magnetic rack that enables the removal of waste products tagged with magnetic beads as part of DNA library preparation.

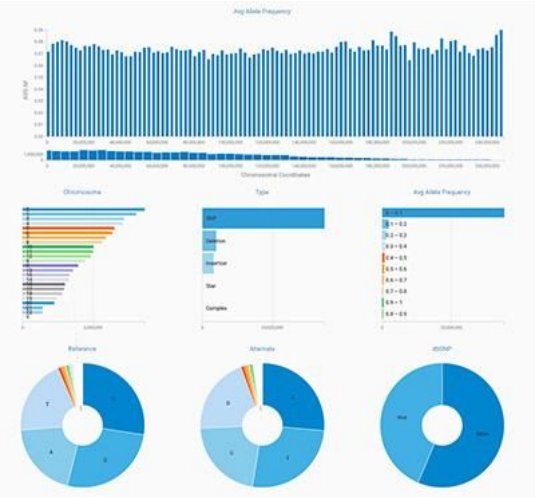
“Our work in the Genomic Technologies Group often requires solutions which are solved by a 'what if?', 3D printing is one of the tools that allows us to translate our imagination into reality,” said Mr Ferguson.

Costing just $20, this customised prototype was considerably cheaper than buying equipment to do a similar job. The team are also experimenting with making a version using the Garvan-Weizmann Centre’s laser cutter, with a view of combining the best pieces from each.

“The 3D printer and laser cutter are only tools to make an idea come to life, the ideas are the core here,” said Mr Li.

James Ferguson with his 3D printed magnetic rack.

Vectis



Vectis, an integrated genomics platform developed by KCCG, is set to provide Australian Genomics Health Alliance (AGHA) members with the capability to house, query and analyse genomic data for its dozen flagship cohorts through VariantAtlas.

Vectis includes a number of open source modules and tools to support the visualisation and analyses of genomes from patient cohorts.

It was first released in December 2016 to house the genomes in the first phase of the Sydney Genomics Collaborative’s Medical Genome Reference Bank (MGRB).

Both VariantAtlas and the Sydney Genomics Collaborative site include features to meet the needs of clinicians, patients, scientists and bioinformaticians, including:

- Search: Query specific chromosome co-ordinates, gene names and annotations in a cohort
- Beacon: Locate specific variants in studies across the Global Alliance for Genomics and Health Beacon Network
- Variant annotations: Including links out to the original supporting evidence
- Explore: Interactive real-time exploration of cohort summary statistics, including variant type, average allele frequencies, and reference and alternate alleles.
- Clinical filtering: subset patients based on clinical attributes and query specific genotypes at the individual level

Dnaerys, a new scalable variant store that works with Vectis, will soon add to these capabilities by allowing users to easily filter patients based on multiple clinical traits and genetic variants.

Vectis and Dnaerys were built by KCCG's Cohort Informatics Team of Dmitry Degrave, Shane Husson, and led by Dr Warren Kaplan.

The team already have new capabilities on the horizon, inspired by collaborative projects emerging across KCCG and discussions with the AGHA. These include increasingly complex queries for discovering new genotype-phenotype associations and managing cancer genomes.

Staff profile

Ahmed Muaz - Principal Software Engineer

Ahmed Muaz is a principal software engineer in our Phenomics team, with expertise in text mining and natural language processing. Ahmed has worked in machine learning for 12 years across localisation, gaming, consumer products feedback, banking and media monitoring, before joining KCCG to apply his skills to medical research.

"I wanted to be involved in research as opposed to just routine software development, and KCCG is the perfect platform to do research and development simultaneously," said Ahmed.

Since starting in June, Ahmed has worked on developing a pipeline to streamline the extraction of information from published scientific literature, particularly information on the relationship between genes, phenotype and disease.

His knowledge of the intricacies of natural language processing and big data handling have helped him enormously in this project, as has his talent for research and passion for healthcare.

"The feeling that whatever we build or develop here can be used to solve unanswered questions or even lead to a cure for someone is extraordinary," said Ahmed.

Ahmed's work in KCCG is constantly evolving and presenting new challenges, and relishes the freedom he is given to come up with his own creative solutions to these problems.

"So far it's been an amazing journey. I'm looking forward to building more technology solutions that can be used to help our cause."

Grants and awards

A/Prof Marcel Dinger, Bronwyn Terrill, Education and Communication Program leader, together with Dr Kate Patterson, Visual Science Communicator at Garvan were awarded a Garvan-Weizmann grant: "Learning with molecular animations:

Teacher roles in knowledge transformation" together with Professors Ron Blonder and Anat Yarden from the Weizmann Institute of Science.

Dr Martin Smith, Genomic Technologies Program leader, together with Dr Igor Ulitsky from the Weizmann Institute of Science and Prof John Mattick, Garvan Director, were awarded a Garvan-Weizmann collaborative grant: "Long Noncoding RNAs Activated during Regeneration in Peripheral Nervous System".

The Informatics team are finalising a computing infrastructure procurement from a Garvan Weizmann Centre for Cellular Genomics grant. While primarily designed to provide differentiating computing resources to the Garvan Weizmann Centre, spare capacity of the infrastructure will also be able to support other strategic genome initiatives at Garvan, including KCCG.

Partnerships

Clinician education resources
KCCG has partnered with the Centre for Genetics Education and Bioplatforms Australia to develop an online educational resource for clinician-researchers who are interested in doing genomics research. It will cover diverse topics including bioinformatics, genomic technologies and ethical considerations. It is expected to be complete in early 2018.

We will also be collaborating with the Royal Australasian College of Physicians (RACP) on a complementary online module to introduce medical specialists to clinical genomics. This resource aims to help specialists appropriately discuss genomics with patients, refer patients to genomic testing and be involved in its broader integration into healthcare. The module is also planned for release in 2018.

Publications and conferences

Publications

Dr Brian Gloss, Beth Signal and A/Prof Marcel Dinger, along with researchers from the University of Cambridge, the University of Lausanne and the University of Queensland published a paper on coding and noncoding RNA expression dynamics. The paper, High resolution temporal transcriptomics of mouse embryoid body development reveals complex expression dynamics of coding and noncoding loci, was published in *Scientific Report*s on 8 June.

KCCG researchers contributed to a paper led by researchers, clinicians and staff in the WA Department of Health, on Initiating an undiagnosed diseases program in the Western Australian public health system in the *Orphanet Journal of Rare Diseases*, published on 3 May. Authors from the KCCG include Dr Tudor Groza, Prof Andreas Zankl and A/Prof Marcel Dinger.

Dr Martin Smith collaborated with researchers at the Garvan Institute on a paper on the RNA modification landscape in human disease, which was accepted for publication in *RNA* on 25 August.

Conferences

Tanya Dwarte and Bronwyn Terrill presenting at the Human Genetics Society of Australasia Annual Scientific Meeting

Australian Genomics National Conference

A/Prof Marcel Dinger presented on the Sydney Genomics Collaborative at the *Australian Genomics National Conference* in Brisbane on 4 August .

Members of the Informatics team (Dr Warren Kaplan, Dmitri Degrave, Shane Husson, Derek Lin and Manuel Sopena-Ballesteros) presented a poster at the conference, on KCCG's Vectis cohort analysis platform.

Human Genetics Society of Australasia Annual Scientific Meeting

KCCG had a strong presence at the *Human Genetics Society of Australasia Annual Scientific Meeting* in Brisbane, 5-8 August.

Dr Lisa Ewans gave two presentations titled 'PLOD3 mutations result in a Stickler syndrome-like connective tissue dysplasia' and 'Genomic sequencing reanalysis at 12 months boosts Mendelian diagnosis and is cost-effective in intellectual disability'.

Bronwyn Terrill, Education and Communication Program leader, gave a presentation based on the Genomics: National Insights of Australians (Genioz) study findings, 'The more I know about genetics...: research to inform Australian community conversations about personal genomics'.

Master of Genetic Counselling student Tanya Dwarte presented on 'the evolving landscape of genetic counselling in the genomic era'.

Others

KCCG Tumour Genomics researcher and intern, Marc de Massy, presented on "Reconstructing advanced lung cancer evolution from whole-genome sequencing" at the *Australian Society for Medical Research NSW Scientific Meeting* on 2 June.

KCCG Tumour Genomics and Clinical Genomics researchers gave talks and posters at the *Sydney Bioinformatics Research Symposium* on 13 June at the University of Sydney. Dr Clare Puttick on identifying runs of homozygosity in whole genome data; Dr Andre Minoche on identifying clinically relevant structural variants from whole genome data; and Marc de Massy on whole-genome sequencing in advanced lung cancer.

Bronwyn Terrill took part in a broadcast STEM pathways panel for secondary schools at the Museum of Arts and Sciences in June. Ms Terrill also led a workshop at the *Australian Science Teachers' Association Conference* in Hobart on 10 July. This furtherdeveloped KCCG's plans for professional development for secondary school science teachers in genomics.

A/Prof Dinger presented on 'Genomics in the clinic: A revolution for healthcare and medical research' at *HISA* in Brisbane on 7 August, as well as at *Disrupt Healthcare* in Melbourne on 28 August.

Dr Mark Cowley, Tumour Genomics Program leader, gave an oral presentation on translating cancer genomics to the clinic at the *Sydney Catalyst International Translational Research Symposium* on 8 August.

Dr Tudor Groza, Phenomics Program leader, gave an oral presentation titled "Towards a comprehensive patient data lifecycle in rare disorders" at the *Undiagnosed Diseases Network International Meeting* in Stockholm on 30-31 Aug. Dr Groza also presented on "Clinical deep phenotyping and its applications" at the 2017 Biohackathon, in Tokyo on 10 Sept.

Dr Warren Kaplan, Informatics Program leader, gave a presentation to a Data Science Group at the Commonwealth Bank, speaking on the computational prospects and challenges of genomic analysis in medical research.

In the media

We have reached 1,000 followers on Twitter! You can follow us here for more insights into our work.

KCCG and Genome.One have reached the amazing milestone of sequencing more than 15,000 genomes, which was announced on the Garvan website on 27 July.

AARNET have published a case study and online story focused on KCCG's genomics capacity and capability to transform lives.

We were also featured in an article in the Australian Healthcare IT news about genomic research, data sharing and the implications for individuals and society.

The Australian Genomics Health Alliance announced the adoption of the KCCG Vectis platform to support data storage, querying and analysis for the Alliance's national genomic cohorts on 21 September. Read our Technology Updates to learn more about Vectis.

Events

Bloody Long Walk

On Sunday 24 September, seven dedicated members of the KCCG team woke up very early to do the Bloody Long Walk, a 35km trek from Maroubra to Circular Quay for Mitochondrial disease.

Mitochondrial disease is an inherited, chronic condition with diverse symptoms, ranging from muscle weakness to seizures and diabetes. Prevalence is estimated at 1 in 5000 people, but the real figure could be much higher.

Mitochondrial disease is one of KCCG's major focus areas. Through whole genome sequencing, we are getting better at providing molecular diagnoses. However there are currently few treatment options, and with symptoms and progression differing greatly between individuals, the disease is not well understood.

The team raised almost $2,500 for the Australian Mitochondrial Disease Foundation to help find therapies and support families affected by this disease.

Mark Cowley, Marcel Dinger, Marie-Jo Brion, John Grady, Manuel Sopena-Ballesteros, Clare Puttick and Bronwyn Terrill finishing the Bloody Long Walk.

Gattaca at National Science Week

Bronwyn Terrill, Education and Communication Program leader, partnered with Australian Health Ethics (previously Centre for Values, Ethics and the Law in Medicine - VELiM) at the University of Sydney to run a series of screenings of the science fiction film Gattaca across Australia in August.

The screenings were followed by lively panel discussions about science, ethics, art and the world portrayed in this 20 year old film.

More than 850 people registered for the screenings and hundreds participated in the panel and online discussions.

Dr Mark Cowley and A/Prof Marcel Dinger were both panelists.

The events were part of National Science Week, with funding by the Australian Government's Inspiring Australia – Science Engagement Programme.

Gattaca screening at the University of Sydney as part of National Science Week

Genioz forums

The *Genomics: National Insights of Australians* (Genioz) program ran public forums alongside the Gattaca screenings. These involved discussions with members of the public about their understanding and perceptions of personal genomic testing. The Genioz study is the first large scale Australian study to explore attitudes towards personal genomics. As well as these public forums, the Genioz researchers have already conducted focus groups, a national survey and interviews.

The research will help define educational strategies and inform national policy, to support the Australian public in making informed decisions in their use of personal genomic technologies.

Bronwyn Terrill is a partner investigator on the Genioz study, which includes Australian and international researchers who work across genomics, education, ethics, genetic counselling and communication worldwide.

Seminars

Our Tumour Genomics Program hosted a special seminar by Prof Edwin Cuppen, Director of the Hartwig Medical Foundation in the Netherland, on 20 June. An expert in whole genome sequence analysis, Prof Cuppen spoke about "National scale cancer genome sequencing in the Netherlands." The Hartwig Foundation is working towards stratifying cancer patients into targeted treatments based on whole genome tumour sequencing and ultimately aims to offer this to all relevant cancer patients in the Netherlands.

We also hosted a special seminar with Prof Makoto Suematsu on the "Mission of AMED: Global data sharing in biomedical sciences" on 6 October. Prof Suematsu is the Founding President of the Japan Agency for Medical Research and Development, and Professor of Biochemistry at Keio University School of Medicine. He specialises in biochemistry and metabolomics research.

Welcoming new team members

The Genomic Technologies group has welcomed two new staff. Dr Kirston Barton joined as their Genomics Application Developer in August, and Shaun Carswell started this week as their Production Bioinformatics Engineer.

If you would like to receive our quarterly newsletter, please sign up here. You can also connect with us on Twitter and LinkedIn.