AUGUST 2016 | Published by RCPA

Issue #061

In This Issue

Interesting Facts

27 July 2016

The day Australia's first whole-genome sequencing service was launched in Sydney.

About 80%

The proportion of rare diseases that are genetic in origin.

Welcome to the August edition of ePathWay

Australia's first Centre for Clinical Genomics was launched last month in Sydney. We caught up with the centre's inaugural Chief Medical Officer, who is also a RCPA Fellow, to find out why this centre will be a game changer for medicine.

Our other stories cover:

- A round up of where we are up to with HIV/AIDS.
- Musculoskeletal biobanks and how their deposits change lives.
- Trachoma and why it still blights some Aboriginal communities.

Heads up - International Pathology Day is Wednesday 16 November this year. Check out the website to see what is being organised and to find out how you can participate.

Don't forget to check the topical posts on our Facebook page and follow our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA) on Twitter to keep up to date with pathology news.

First clinical whole-genome sequencing service offers new hope to thousands of patients and their families

6-8%

The estimated proportion of Australians that are affected by a rare disease.

Source: Garvan Institute

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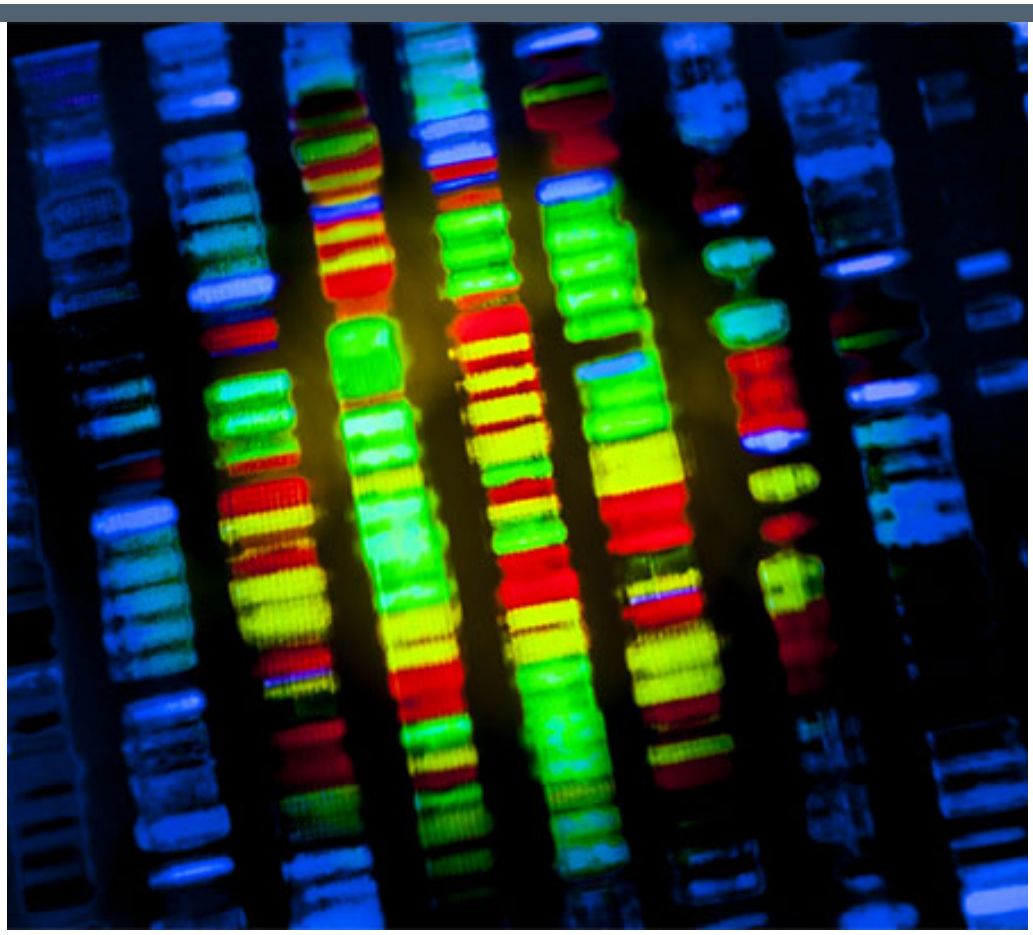

Australia's first clinical whole-genome sequencing service, located at the Garvan Institute of Medical Research's newly opened Kinghorn Centre for Clinical Genomics (KCCG) in Sydney, was officially opened on July 27 this year. KCCG's inaugural Chief Medical Officer, RCPA Fellow Professor Leslie Burnett, explains why this new service is another game changer for medicine.

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We're still waiting to bowl the final strike against HIV/AIDS

It's been 30 years since *those* ads appeared where the Grim Reaper hurled bowling balls towards people who risked becoming infected with Human Immunodeficiency Virus (HIV). It then took 10 years for us to start bowling a few balls of our own back, and we're still waiting to bowl the final strike.

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First clinical whole-genome sequencing service offers new hope to thousands of patients and their families

The Whole Genome Sequencing machine (Illumina X ten) about to send information to the bioinformatics supercomputer 'pipeline'

Australia's first clinical whole-genome sequencing service, located at the Garvan Institute of Medical Research's newly opened Kinghorn Centre for Clinical Genomics (KCCG) in Sydney, was officially opened on July 27 this year. KCCG's inaugural Chief Medical Officer, RCPA Fellow Professor Leslie Burnett, explains why this new service is another game changer for medicine.

"Thanks to a significant donation we have the world's first Illumina HiSeq X Ten sequencing platform which means we can sequence about 16,000 whole human genomes each year," he explains.

"There is a large backlog of people who will benefit from this capability so we have prioritised families of children with undiagnosed genetic disorders to access this service first. This is because these families have often been on a long and difficult diagnostic odyssey and have drawn a blank in terms of finding a diagnosis."

"Our service, offered through a newly established health information company called Genome.One, looks for the genetic variant responsible for their disorder. This means these families could finally have a diagnosis and the ability to access the right treatment pathways faster."

This Australian funded service is the result of a two and a half year development in association with the country's largest provider of public pathology services, NSW Health Pathology.

Prof Burnett says the whole-genome sequencing service has so far increased the diagnosis rate of these rare genetic disorders from 20% to between 40 and 60%, and he expects this rate to increase further as their knowledge base expands.

Professor Leslie Burnett

“This is just the beginning of what we can do, and it’s the equivalent to discovering antibiotics in terms of its significance. This work takes extraordinary expertise, and we have needed to assemble a specialised team of nearly 50 genetic pathologists, laboratory scientists and Information Technology specialists to drive it.”

The KCCG is only the second accredited facility in the world (the first outside of the USA) for whole-genome sequencing.

“We chose to use National Association of Testing Authorities (NATA)/ RCPA accreditation, and we received our accreditation on July 12 this year. This was a rigorous process to ensure our laboratory operates at safe standards for patient care. As part of this process we sequenced more than 100 whole diagnostic genomes, and were examined by a NATA/RCPA-assembled team like no other!”

So what does it take to sequence a whole genome?

“It’s nothing like you see on TV shows such as CSI where they get an answer in about an hour. It takes between eight to 12 weeks from sample to report for each patient, including genetic counselling to prepare patients for potentially unexpected results," explains Prof Burnett.

"To perform the test we take a blood sample and a cheek swab from the patient, and also from their parents if possible, and we determine the full six-billion DNA letters of these samples. From this, we generally find about four million genetic sequence differences from the average ‘reference’ sequence. We then filter them down to 1000s, then to about 200, and this is when they are inspected manually to derive the short list of candidates causing the genetic disorder.”

While the KCCG is Australia-based, it is also looking to work with other local and international clinical and research communities to expand the knowledge of the human genome. This will hopefully open more avenues to explore in the genomic revolution that Prof Burnett is excited to be a part of.

“When I was a medical student 40 years ago genetic sequencing was just starting and I thought it would reach clinical medicine ‘soon’. But ‘soon’ stretched into years, and then decades. Now we are sequencing the whole genome, and I’ve lived to see it and be a part of it. It’s certainly an exciting time to be at the forefront of medicine.”

Families who are currently searching for a diagnosis of a genetic disease should speak to their genetic specialist about whether Genome.One’s new test is appropriate for them. To enquire about the clinical service, email enquiries@genome.one or phone +61 2 9359 8002.

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"The big breakthrough for HIV hasn't happened yet, but it was 1996 when the game changed," explains Associate Professor Roger Garsia, Head of the Central Clinical School at the University of Sydney and Director of HIV for Sydney Local Health District.

"That was when we saw a decrease in the number of HIV-infected people in hospitals due to more effective combination therapy, and the death rate from AIDS (acquired immune deficiency syndrome) started to decrease."

These days HIV and AIDS, which develops in more than 95% of cases if HIV is left untreated, has dropped off the radar of many doctors in Australia and New Zealand. A/Prof Garsia says this is probably due to the fact we no longer have significant numbers of HIV-infected people in acute hospital care, but that's not the case in many other countries.

"Advanced HIV and AIDS is still a major burden on hospital facilities in many countries. Globally, less than 50% of HIV-infected people know they have it, and too few individuals are tested, identified and treated for preventive measures to have much impact on the rate of transmission," he explains.

"However, there has still been a significant impact on death rates internationally with total deaths from AIDS peaking in 2004, a decade after they peaked in Australia and other western countries. Late

diagnosis followed by prompt treatment will still allow immune recovery, but unfortunately the transmission cycle will have usually already occurred."

He says Australia and New Zealand do have good testing rates that show continuing evidence of new infections occurring. To successfully impact on these, many high-risk people, including HIV negative men-who-have-sex-with-men (MSM) who remain at risk, could potentially be prescribed antiretroviral therapy as a preventive or prophylactic measure without being part of a trial. This would require modifying the approved indications for antiretroviral drugs to include prophylaxis. One pharmaceutical company has already applied for listing of a drug for HIV prophylaxis on the Pharmaceutical Benefits Scheme (PBS).

"The effectiveness of this approach has been confirmed through trials, and there are now further studies underway both locally and internationally looking at how well this approach would be accepted by high risk groups and the impact it would have on both HIV and STI rates. There are similarities in this method to taking the oral contraceptive pill to prevent pregnancy when risk is sporadic, and there is work going on to determine for how long an HIV-positive individual must be treated before their risk of transmitting the virus is effectively lowered," says A/Prof Garsia.

He says the Pre-exposure prophylaxis (PreP) approach may also have a role for people who are travelling in countries with highly endemic HIV. The pharmaceutical industry is also exploring slow release prophylactic injections that might last 100 days or more.

When it comes to testing for HIV, A/Prof Garsia says Point-of-Care tests (PoCT) and rapid HIV tests in walk-in centres are useful to reach people who may not accept testing through a traditional medical centre, as long as the tests are done in a quality framework.

"In Africa for example, some of the population won't accept testing at health centres but will agree to a PoCT at home. In contrast, Australia's population has access to very high quality laboratory testing, so it would be fair to say the uptake of PoCT testing is modest. Most HIV tests here are performed on venous blood samples sent to a laboratory, and this is a good approach as it allows for other STI testing at the same time."

He says other options being explored in the HIV prevention space include embedding neutralising HIV antibodies in microbicide preparations in the form of a protective gel applied vaginally before sex.

"We hope to see some advances in HIV vaccine development over the next five to 10 years, however, the results of the search for a truly effective vaccine are still disappointing."

While these strategies may seem like significant breakthroughs, A/Prof Garsia says since the leaps forward of the mid 1990s, there have been only incremental gains in the area of HIV therapy, but no real ground breaking changes yet. So what does the big HIV breakthrough look like?

"It would be a drug that truly eliminates the virus from already infected cells, but we're still decades away from that."

HIV was also covered in the August 2014, February 2013 and July 2011 editions of ePathWay.

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In terms of musculoskeletal materials, Mr Poniatowski says the DTBV collects and stores bone, cartilage and tendons for up to five years for surgeons to use as tissue transplants when required.

“If people have an injury such as an anterior cruciate ligament (ACL) tear in their knee, then surgeons can replace that ligament with tendons that we store in our tissue bank. We can also provide cartilage for other types of injuries, but we don’t get many requests for it,” he explains.

Mr Poniatowski says they try to accommodate requests from surgeons which might rarely include meniscus (fibrocartilage cushions in the knee) and osteochondral cartilage, but both of these need to be ‘size matched’ before they can be used.

“We try to find out what surgeons need and tailor our collection for them. We also collect bone that surgeons would otherwise discard after a hip replacement, and we mill it up into granules. This can then be used to pack into holes in damaged and diseased bones when required.”

A/Prof Ranson says this material is like scaffolding, and the recipient’s own bone grows into this donated bone tissue over time.

"Musculoskeletal donations may not save lives in the same way a heart or lung will, but they certainly improve a person's quality of life and in this way they can transform a person's life," he explains.

"We are very careful about screening the source of our donations. Out of over 6,000 potential donors each year, our screening and checking processes reduce that to about 100 successful donors."

Apart from bone removed during surgery, the main source of donations is deceased people, and this is why the DTBV and the Victorian Institute of Forensic Medicine (VIFM), where A/Prof Ranson is Deputy Director, work closely together.

"The VIFM has privileged access to a large group of deceased people whose deaths have been reported to the Coroner. Our job is to investigate these deaths, and looking at their medical history is one a part of what we do. We are very careful to check potential donors to make sure they are disease and hazard free," A/Prof Ranson explains.

"One of our challenges is that the donors are usually people who were healthy and who died unexpectedly, and we need to retrieve their potential donor tissue within 24 hours of death, but we can only do this with the consent of the next of kin," explains Mr Poniatowski.

"If people have not heard of a tissue donation, then talking to a relative about donating their deceased relative's tissue can be difficult when they are grieving and in a sensitive state. This is why education about the benefits of tissue donation is very important to help inform a family's decision about donation at a very difficult time."

People probably don't realise how much of a difference these donations can make until they need to make a 'withdrawal'. For example, if you hear a crunch or snap on the field this season, it's not always game over for that player thanks to the valuable deposits so generously donated and then stored in facilities like the DTBV.

Check out the DTBV and Donate Life websites to find out how to become a tissue donor.

Organ and tissue donation was also covered in the November 2015 edition of ePathWay.

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"Trachoma is an infectious disease that is spread by touch such as rubbing infected eyes with hands and then touching another person. It is also spread by flies that have been in contact with the eyes of infected people.

Associate Professor Rob Baird, Infectious Diseases Physician and Director of Pathology for Territory Pathology in Darwin, says trachoma is still primarily a disease of poverty, and is usually diagnosed based on direct inspection of the eye.

"As trachoma is a clinical diagnosis, pathologists don't often receive specimens to test for the pathogen outside of research trials. When we do test for it, ocular chlamydia (trachoma) can be detected by the same assays usually used to diagnose patients with genital chlamydia. It's therefore necessary to recognise that detection of chlamydia DNA can come from ocular or genital sites."

A/Prof Baird says trachoma's causative pathogen *Chlamydia trachomatis* (an obligate intracellular pathogen) is the same bacterial species that causes the sexually transmitted infection (STI) chlamydia, but the diseases are caused by different *Chlamydia* serovars. Ensuring the correct clinical diagnosis is therefore important, especially if it involves a child.

“For instance, if a patient has trachoma, rubs their infected eyes, and then touches their genitals, the genital swab could potentially be positive for chlamydia and the result open to misinterpretation. This is because most commercial nucleic acid assays to detect chlamydia don't distinguish between clinical disease serovars.”

He says most chlamydia testing is now DNA based, and can detect the organism on a swab up to two weeks after the causative organism has been eliminated by antibiotics.

While most people can clear a one off infection, years of repeated infections can result in severe scarring on the inside of the eyelid (trachomatous conjunctival scarring), causing it to turn inwards. This enables the eyelashes to rub against the eyeball (trachomatous trichiasis) resulting in persistent pain, light intolerance, and scarring of the cornea. If it’s not treated this leads to irreversible opacities resulting in visual impairment or blindness.

“Direct inspection of the eye allows grading of the infection and scarring of the eye to be assessed. This eye damage is present even if a current active infection is not, hence the limited role for diagnostics,” explains A/Prof Baird.

The World Health Organization (WHO) adopted a resolution in 1998 that targets the global elimination of trachoma as a public health problem by 2020. The elimination strategy is captured by the acronym SAFE:

Surgery for advanced disease

Antibiotics to clear the infection

Facial cleanliness

Environmental improvements to reduce transmission.

In 2009, the Australian Government committed to eliminate blinding trachoma from Australian Aboriginal communities by 2020 in accordance with the WHO Global Elimination of Trachoma program (GET 2020).

Why is trachoma a disease of poverty?

It persists in places where there are poor living standards and poor community and personal hygiene standards, often due to inadequate access to functioning washing facilities and bathrooms. Trachoma is still a public health problem in many of the poorest and most rural areas of 42 countries, including Australia, which is the only developed country on this list.

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