



# PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



MARCH 2018 | PUBLISHED BY RCPA

ISSUE #078

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- Newborn screening for primary immunodeficiency diseases is a health priority
- The largest genomic datasets provide researchers with an important resource for the future
- Australian team first in the world to use the whole epigenome and single cell genomics to study rare breast tumours

## Welcome to the March 2018 edition of ePathWay



## INTERESTING FACTS

### 3.5 months

It has been demonstrated that outcomes are markedly improved for infants diagnosed with Severe Combined Immunodeficiency (SCID) who undergo hematopoietic stem cell transplantation (HSCT) prior to this age.<sup>1</sup>

### 300+

The number of distinct genetic molecular abnormalities

Pathology Update 2018, A Bridge to the Future, is over after another successful year. Once again, we would like to thank all of the international and local speakers who joined the conference this year, and the 1,326 delegates who travelled from far and wide to attend. International delegates travelled from Canada, China, Fiji, Germany, Israel, Kiribati, Malaysia, New Caledonia, New Zealand, Singapore, Switzerland, Tonga, UK, USA and Vanuatu. Also, thank you to the Chair and Members of the Overseeing and Scientific Program Committees who helped to make the event a success.

Please note that delegates can provide session feedback via the Pathology Update app. If you haven't yet downloaded the app and would like to do so, please search 'RCPA' in your app store or follow [this link](#).

Post-conference information and details of all the winners can be viewed [here](#). The official conference photos are available to view and purchase [here](#).

We are sure you will agree that the 14 international and 140 Australasian speakers at Pathology Update 2018 were

resulting in primary immunodeficiency diseases (PID).<sup>1</sup>

**58,000**

The number of births internationally that are affected by SCID, commonly referred to as the 'bubble boy' disease.<sup>2</sup>

Source:

[1] Jovanka King, Jonas F. Ludvigsson, and Lennart Hammarström, *International Journal of Neonatal Screening*, 3 August 2017

[2]

<https://www.smh.com.au/healthcare/doctors-want-newborns-to-be-screened-for-bubble-boy-scid-disease-20180301-p4z2bc.html>

outstanding. From the wide selection of informative and thought provoking presentations given during the three day conference, we chose four for this month's edition of ePathWay.

We will take a look at:

- New treatments designed to lower levels of lipoprotein (a);
- Newborn screening for primary immunodeficiency diseases as a health priority;
- The largest genomic datasets providing researchers with an important resource for the future; and
- The Australian team that is first in the world to use the whole epigenome and single cell genomics to study rare breast tumours.

After two successful years at ICC Sydney, it's time to start alternating again, therefore we look forward to seeing you in Melbourne for Pathology Update 2019!

Remember to follow us on [Facebook](#) (@TheRoyalCollegeofPathologistsOfAustralasia), Twitter (@PathologyRCPA) or on Instagram (@the\_rcpa). CEO, Dr Debra Graves can be followed on Twitter too (@DebraJGraves).

## IMPORTANT MESSAGE



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**New treatments designed to lower levels of lipoprotein (a) – a major risk factor for cardiovascular disease**

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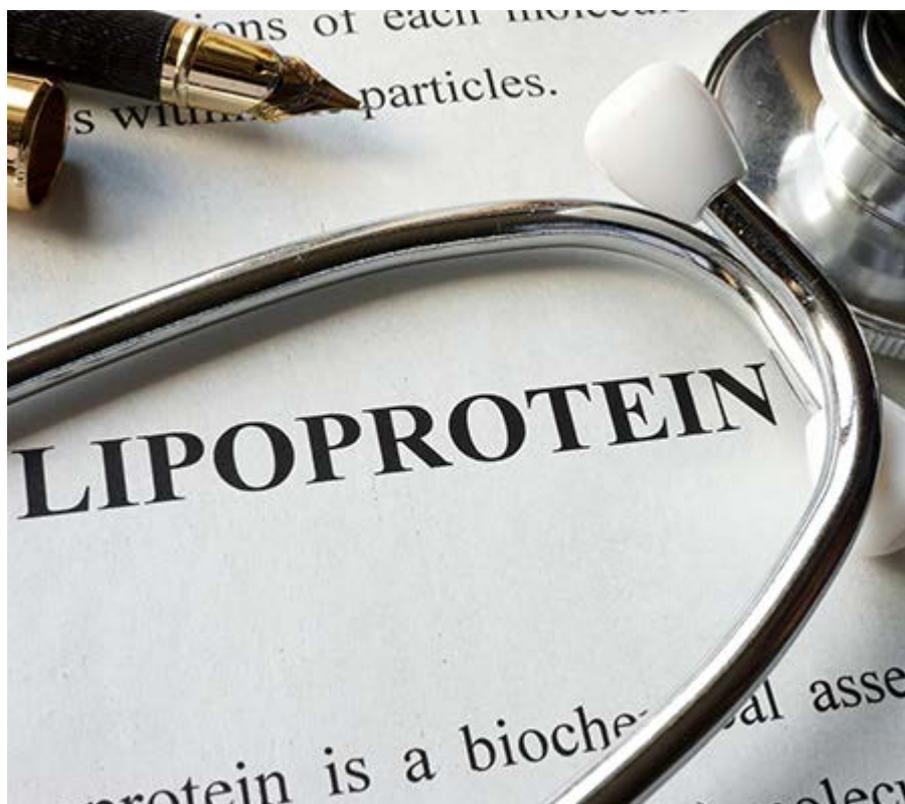
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New insights into lipoprotein (a), a cardiovascular risk factor that affects 20% of the population, have yielded a breakthrough in newly created, effective treatments therefore further increasing the need to both understand and measure this entity.

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## Newborn screening for primary immunodeficiency diseases is a health priority

At Pathology Update 2018, Dr Jovanka King explained why she recommends that newborn screening be expanded to include testing for severe immunodeficiency diseases. Dr King discussed her research on strategies for screening newborn babies for primary immunodeficiency diseases (PID), including Severe Combined Immunodeficiency (SCID), a life-threatening condition where babies are born without a functional immune system.



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## The largest genomic datasets provide researchers with an important resource for the future

Professor David Thomas discussed preliminary findings from the Medical Genome Reference Bank (MGRB) program at this year's Update. The Australian study is already one of the largest genomic datasets ever produced in the country, and the largest dataset on the well elderly worldwide. The MGRB program is sequencing and analysing genomes from healthy, aged individuals to create a database that is depleted of damaging genetic variants. The study aims to provide a universal 'control' set for future disease-focused genomic research, whilst offering unique insights into the ageing process.



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## Australian team first in the world to use the whole epigenome and single cell genomics to study rare breast tumours

Professor Sandra O’Toole, breast cancer researcher and pathologist at the Garvan Institute of Medical Research, explained that, in a global first, an Australian team has used cutting edge technologies for whole genome epigenetic analysis and single cell genomics to study phyllodes tumours, a rare type of breast tumour.



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## Previous Editions



**IN THIS ISSUE**

- The optimal balance between salt reduction and the elimination of iodine deficiency disorders
- The best protection against the 2018 flu season is to get the vaccine
- Proliferations of synthetic drugs – an emerging issue for toxicology in Australia

**Welcome to the February 2018 edition of ePathWay**

Pathology Update 2018 is nearly upon us, when hundreds of pathologists will once again congregate at ICC Sydney on 2 March 2018 for three days. This year, the conference will feature 14 outstanding international speakers and a contingent of over 140 Australasian speakers. The College would like to thank its international and local speakers for the time and efforts involved in preparing their presentations. Also, thank you to all of the delegates who will attend, making Pathology Update one of the foremost international pathology conferences.

In this month's issue of ePathWay, we will look at:

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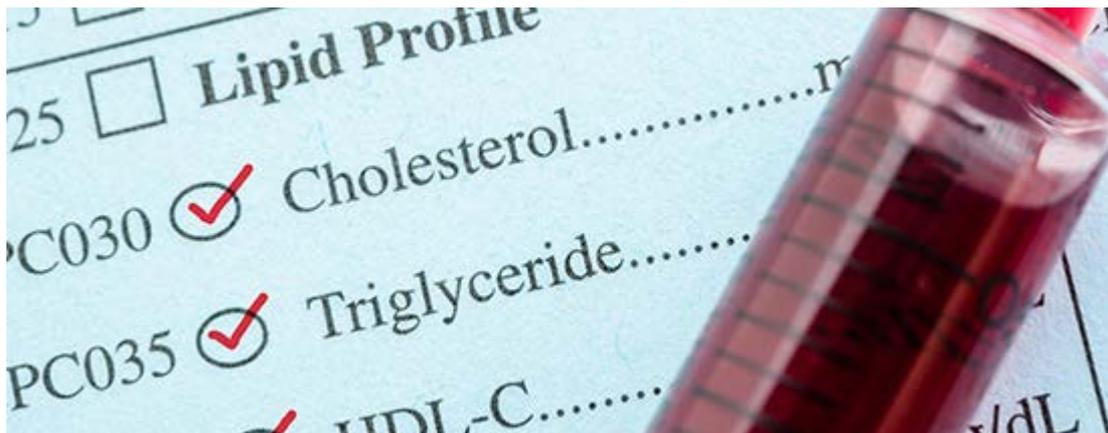
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## New treatments designed to lower levels of lipoprotein (a) – a major risk factor for cardiovascular disease



New insights into lipoprotein (a), a cardiovascular risk factor that affects 20% of the population, have yielded a breakthrough in newly created, effective treatments therefore further increasing the need to both understand and measure this entity.

A/Prof David Sullivan, Head of Chemical Pathology at Royal Prince Alfred Hospital, said,

“We have known for a long time that lipoprotein (a) is a source of a substantial proportion of cardiovascular disease. There are six or seven mechanisms where lipoprotein (a) can cause substantial harm to an individual. This damage, which is associated with blood clotting, is known to cause the blockage of arteries and heart valves, including the aortic heart valve. These complications are proportional to an individual’s levels of the entity, lipoprotein (a). Over the past 30 years, we have had a limited scientific understanding of lipoprotein (a) and, typically, it was very difficult to measure for a variety of reasons.

“With such a significant proportion (20%) of the population affected by this, it is an issue of great interest in Australia and around the world. The level of lipoprotein (a) appears to be determined by an individual’s gene inheritance. In the past, we have been able to inform patients of their levels of lipoprotein (a), however it was very difficult to provide any effective treatment.

“Cholesterol treatments such as statins did not reveal any beneficial results at lowering levels of lipoprotein (a). When necessary, we provided a huge dose of a very old

treatment called nicotinic acid (also known as vitamin B3), and which can be very unpleasant in itself.”

A/Prof Sullivan explained that now, for the first time, newer anti-heart disease, cholesterol-lowering drugs are showing success at effectively lowering lipoprotein (a). Also, using some of the lessons learned with these drugs, new treatments have been developed which are specifically designed to reduce the levels of this material quite considerably.

“A newly invented treatment called PCSK9 antibody treatment has proven to be highly effective in lowering cholesterol and preventing heart disease. It also happens to be useful at reducing lipoprotein (a) by around 20-30%, which is a useful start. By using some of the very advanced techniques for lowering blood fats, we should be able to lower the specific blood fat carrying material by up to 90% using a technique called antisense oligonucleotides.”

To receive the new treatments, an individual would be selected due to history of heart disease and the need to lower cholesterol levels. Individuals who could benefit from this are those who have had a heart attack or a stroke at a young age and the usual causes have been excluded. If an individual is not a smoker and they do not have particularly high blood fats, then it would be worthwhile to assess their levels of lipoprotein (a). Also, individuals from families with hereditary high cholesterol levels could benefit from having their lipoprotein (a) levels measured.

A/Prof Sullivan explained that further research into lipoprotein (a) is required in order to enhance our understanding of its effects, which will result in more effective treatments specific to lowering the levels of this material in patients.

“Despite this success, we still don’t know enough about lipoprotein (a). We sometimes find that it’s elevated in people who don’t have any other explanation for any of their heart attacks and strokes but at the same time, we clearly find that some people tolerate high levels without becoming unwell, so we need to have a much better opportunity to understand exactly how its working and to try and attend to that.” “The new treatment is not currently available on the Medicare Benefits Schedule. We are dedicated to developing more accurate measurements, which are based on the work that has evolved over the years.”

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## Newborn screening for primary immunodeficiency diseases is a health priority



At Pathology Update 2018, Dr Jovanka King explained why she recommends that newborn screening be expanded to include testing for severe immunodeficiency diseases. Dr King discussed her research on strategies for screening newborn babies for primary immunodeficiency diseases (PID), including Severe Combined Immunodeficiency (SCID), a life-threatening condition where babies are born without a functional immune system.

Dr King, a specialist paediatric immunologist and immunopathologist at SA Pathology at the Women's and Children's Hospital, and the University of Adelaide, explained that this additional screening would significantly improve the survival and wellbeing of children affected by these disorders, and expects that it would be cost effective.

"Screening babies for primary immune deficiency disorders, including SCID, and evaluating how these tests can be implemented in each state's newborn screening service should be a health priority in Australia. Conditions such as SCID are life-threatening; therefore, making a diagnosis and starting treatment as early as possible is essential. Achieving a diagnosis is typically delayed; therefore, babies become critically unwell as a result of severe, recurrent infections and other complications. In these cases, they frequently require prolonged hospital and intensive care unit admissions.

"SCID can be cured by a bone marrow or stem cell transplant. There is evidence that if infants with SCID undergo transplantation prior to the age of 3.5 months, their outcomes in terms of survival and long-term health are much improved. Beyond this age, affected babies have a higher burden of infection and other complications due to their untreated

disease. The only realistic way to achieve the goal of early transplantation for babies with SCID is to diagnose them early in the newborn period, before they develop symptoms of the disease. This is only achievable through newborn screening.

“The current process for screening newborns in Australia involves each baby having a heel prick blood test when they are between two and three days old. That blood sample is blotted onto a piece of filter paper, and is sent to specialised neonatal screening laboratories for testing. Babies are currently screened for over 40 different conditions, including inborn errors of metabolism and cystic fibrosis, but with recent technological advances we have the potential to expand this further to screen for other important conditions.”

Dr King’s research has included analysing data from a newborn screening program for PID conducted in Sweden, where almost 60,000 newborn babies were screened for SCID and other forms of PID over a two-year period.

“Our research from Sweden, where I worked previously, has demonstrated that population based newborn screening is an effective way in which to identify babies affected by PID. Affected infants were detected by an abnormal screening test, which enabled rapid medical assessment, confirmatory testing and commencement of treatment within the first weeks of life. This has also been demonstrated in similar studies performed in other countries throughout the world.

“New Zealand recently initiated their screening program for SCID, and almost every state in the United States, and many countries throughout Europe, the Middle East and Asia have initiated successful screening programs for PID, which have become routine. There is a clear need to establish a newborn screening program for PID in Australia,” said Dr King.

In collaboration with other children’s hospitals throughout Australia, Dr King will be conducting a cost benefit analysis which is expected to be completed later in the year. Dr King believes that not only would this new screening test be beneficial for affected infants and their families around the country, it would also be cost effective.

“The biggest barrier to implementing any new testing strategy is cost; however, economic analyses performed in other countries have demonstrated that it is more cost effective to screen newborns for SCID than it is to manage a critically unwell child in whom diagnosis and treatment was delayed.”

For a disease to be included as part of a population-based screening program, it needs to meet certain criteria. The disease needs to be severe, and an effective treatment needs to be available. The testing strategy must also be robust, and have been evaluated on a large scale.

“A retrospective study is underway in our laboratory in South Australia, where we are testing samples from our patients who were diagnosed with PID over the past 17 years. This will determine whether their disease could have been diagnosed in the first weeks of life, and hence if this testing strategy will be effective in our population. Following this, our aim is to secure funding to conduct a prospective screening study, where every baby born in South Australia will undergo screening for these immune deficiency diseases. There are over 300 different kinds of PID and, through our ongoing research efforts, we are also working on new strategies to improve our current capacity to diagnose these severe, life-threatening diseases and improve outcomes for affected patients,” explained Dr King.

During Pathology Update 2018, Dr King’s work was mentioned in approximately 100 media outlets in Australia, including: [The Sydney Morning Herald](#); [The Australian](#); and [NZ Doctor](#).

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## The largest genomic datasets provide researchers with an important resource for the future



Professor David Thomas discussed preliminary findings from the Medical Genome Reference Bank (MGRB) program at this year's Update. The Australian study is already one of the largest genomic datasets ever produced in the country, and the largest dataset on the well elderly worldwide. The MGRB program is sequencing and analysing genomes from healthy, aged individuals to create a database that is depleted of damaging genetic variants. The study aims to provide a universal 'control' set for future disease-focused genomic research, whilst offering unique insights into the ageing process.

The results are providing valuable datasets for health and medical researchers in Australia and around the world and are providing an understanding of genetics in the healthy ageing population. The project, which was funded by NSW Health through the Office for Health and Medical Research, is being undertaken at the Kinghorn Centre for Clinical Genomics (Garvan Institute of Medical Research) in collaboration with two leading Australian research studies in older people: the ASPREE (ASpirin in Reducing Events in the Elderly) study (Monash University, Melbourne) and the 45 and Up study (Sax Institute, Sydney).

Whole genome sequencing of approximately 4000 Australians over the age of 70 years, who do not have any history of cancer, cardio-vascular disease or dementia, is being performed by Genome.One, a wholly owned subsidiary of Garvan, and home to the largest sequencing facility in the Southern Hemisphere.

Prof Thomas, Director of The Kinghorn Cancer Centre and Head of Garvan's Cancer

Division and co-lead of MGRB said,

“We hope this dataset will help us understand what genetic variants cause disease, by filtering out the vast amount of genetic variation that we carry that is compatible with a long, healthy life. We will use the MGRB as a control for understanding genetic risk in young people with cancer. By contrasting the extremes, we get more power to understand the genetic basis for disease.

“For example, approximately 5% of the elderly cohort appears to have what we might currently think of as clinically significant genetic findings, but without any overt evidence of disease. This finding is important information in interpreting the same genetic variant when found in a young person, to help decide its clinical meaning.

“The study, which has already generated a vast amount of genomic information, assumes the relative depletion of those ‘risk genes’ (damaging genetic variants) in the population, which normally cause the disease to develop. In addition to studying rare genetic variations that cause clinical syndromes, the MGRB enables study of common variations which are widely present in the community, and which have disproportionate contribution to the risk of common diseases like dementia.

“Just as importantly, we can use the MGRB to understand the genetic basis of health in ageing: do our genes make a difference in how we age? We are beginning to have fascinating insights into what we can learn from the whole genome as we get older.

“We can also observe the ageing process reflected in these genomes, and we’ve made some very interesting observations about features which potentially reflect a person’s biological age more effectively than chronological age.”

As one of the largest whole genome studies of an elderly well population, it is hoped that this Australian study will enable clinicians and researchers to access results that will assist their own clinical interpretation and research.

“We are putting together a major research paper on the first results from the MGRB. A major goal is to create a resource for the clinical genetics and genomic research communities to help them with their own research. We have already received 27 applications from researchers, some as far afield as the U.S, to utilise the data set for their research, which is very promising,” said Prof Thomas.

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## Australian team first in the world to use the whole epigenome and single cell genomics to study rare breast tumours



Professor Sandra O'Toole, breast cancer researcher and pathologist at the Garvan Institute of Medical Research, explained that, in a global first, an Australian team has used cutting edge technologies for whole genome epigenetic analysis and single cell genomics to study phyllodes tumours, a rare type of breast tumour.

The results of this first assessment of genome-wide DNA methylation in phyllodes tumours, offer a unique opportunity to identify biomarkers to better classify phyllodes tumours and good potential for translation into improved treatment outcomes for patients.

Prof O'Toole explained,

“Through early access to new technology, via collaboration with Dr Clare Stirzaker, Prof Susan Clark and their team at the Garvan Institute, we have been able to profile the whole epigenome of phyllodes tumours. We have identified striking differences in the patterns of methylation between malignant phyllodes tumours and the less aggressive subtypes. We hope to exploit these differences to develop a diagnostic test for improved phyllodes tumour stratification.”

Using single cell transcriptomic technology at the new Garvan-Weizmann Centre for Cellular Genomics, together with A/Prof Alexander Swarbrick's team, they have also been able to analyse the very rare malignant phyllodes tumour at a single cell level looking at all of the expressed genes from each individual cell. Previous technology only

allowed study of the whole tumour as a mixture, potentially missing important variations from cell to cell. This technology is especially useful in studying the response of the person (host) to the tumour, for example in determining the types of immune cells present.

The study, which is funded through the National Breast Cancer Foundation and the Sydney Breast Cancer Foundation, has captured 4,500 cells from one highly aggressive malignant phyllodes tumour with an individual reading of each cell. This has provided unique insights into what drives these tumours.

“By introducing cutting edge technology to the analysis of phyllodes tumours, we have been able to analyse the changes at the single cell level to see what makes them tick. In exciting preliminary data, we have observed that inflammation might play an important role in driving these tumours. Although it is early days, we’re hopeful that with more work, an immune treatment approach may prove to be effective, as malignant phyllodes tumours may have a very poor outcome and tend to be resistant to traditional chemotherapy and radiation treatment. We would like to follow up this study on phyllodes tumours, and are seeking funding to be able to study these changes in larger groups of women, a critical step to move this research finding into the clinic,” explained Prof O’Toole.

Phyllodes tumours are rare and there is still currently no effective treatment if the tumours cannot be controlled surgically. By utilising the latest technology to understand phyllodes tumours, it is hoped that the study will offer improved ways to diagnose these tumours.

“For patients with these rare tumours their cancer may be misdiagnosed. The tumours can show considerable variability so a patient may have a biopsy that shows only benign tissue, but the malignant tissue could be missed. If the tumour recurs and cannot be controlled by surgery, there is no effective treatment.

“The importance of research to identify better diagnostic tests and improved treatments cannot be emphasised enough. A good example of this is more common breast cancers - by studying the biological changes in the cancer cells, we understood that the hormones and pathways that drive tumour growth can be blocked. We now have very effective treatments against these types of breast cancer, because we understand the biology.

“Conversely, rare tumours are under-analysed because they are under-recognised and until recently patients haven’t had a loud voice advocating for research. If you were to add up all the individual types of rare and uncommon cancers, as a group, they would become one of the most common cancers. Unfortunately there are far worse outcomes for patients with rare cancers because we don’t know much about them; therefore we can’t diagnose or treat them effectively and therefore further research is absolutely critical,” said Prof O’Toole.

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