THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

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IN THIS ISSUE

- New project ready to tackle mitochondrial disease diagnosis dilemma
- How do you define a pathologist?
- Newborn screening is navigating uncharted frontiers
- Pathology results need context to detect deterioration in a patient's condition

INTERESTING FACTS

1988

The year when mutations in mitochondrial DNA were discovered to cause mitochondrial disease.

1995

The year when nuclear gene mutations were also found to cause mitochondrial disease.

Welcome to the May 2017 edition of ePathWay

A research project about to kick off in Australia is aiming to change the way mitochondrial disease (mito) is diagnosed. Two College Fellows are involved in a collaboration between the Australian Genomics Health Alliance and the Australian Mitochondrial Disease Foundation that looks set to have a big impact on the lives of people with mito.

We are almost at the end of our Pathology Update 2017 coverage as well. The first two articles listed below are from that conference, while our Lay Committee requested the third article:

- Why a pathologist is every patient's doctor.
- Controversies in newborn screening.
- Monitoring and flagging a patient's deteriorating condition.

As always, check in to our Facebook page, review the latest tweets from our CEO Dr Debra Graves (@DebraJGraves) or the College (@PathologyRCPA), to keep up to date with the RCPA and new about pathology.

New project ready to tackle mitochondrial disease diagnosis dilemma

Up to 30

The number of children born in Australia every week who are at risk for developing a mild to moderately disabling form of mitochondrial disease, while at least **one Australian child born every week** will develop a severe or life-threatening form of the disease.

Source: AMDF Fact Sheet: Mitochondrial Disease

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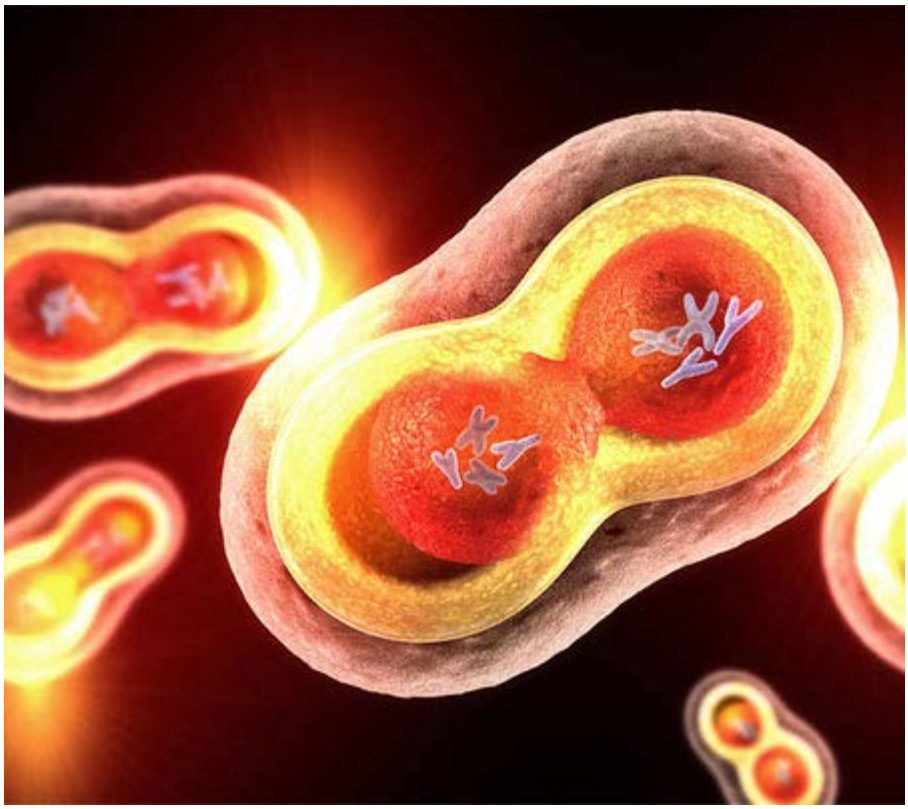

Diagnosing mitochondrial disease (mito) is challenging. The disease manifestations are broad, the diagnostic pathway isn't standardised, and diagnostic tests are often invasive. Genetic testing is accurate and less invasive, but it has been mostly uncoordinated leading to inefficient diagnosis and unnecessary costs. The good news is a research project about to kick off in Australia is looking to change all of this.

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Newborn screening is navigating uncharted frontiers

Newborn screening (NBS) is a public health success, but it is facing challenges created by rapid technological advances that have identified many new candidate disorders that might fulfil criteria for screening. The issues that accompany genetic testing also mean NBS is navigating uncharted frontiers.

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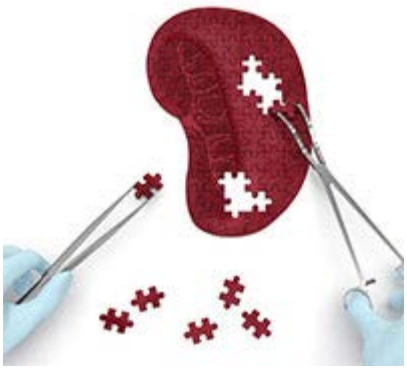
Pathology results need context to detect deterioration in a patient's condition

When it comes to detecting or monitoring the deterioration in a patient's condition, the pathology result is just one piece of information in the whole clinical picture. For example, a 'normal' test result for one person can be a sign of deterioration for another, and that's why clinical context matters.



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Previous Editions

2017

066 - February 2017 | 067 - March 2017 | 068 - April 2017

2016

055 - February 2016 | 056 - March 2016 | 057 - April 2016

058 - May 2016 | 059 - June 2016 | 060 - July 2016

061 - August 2016 | 062 - September 2016 | 063 - October 2016

064 - November 2016 | 065 - Dec 2016/Jan 2017

2015

044 - February 2015 | 045 - March 2015 | 046 - April 2015

047 - May 2015 | 048 - June 2015 | 049 - July 2015

050 - August 2015 | 051 - September 2015 | 052 - October 2015

053 - November 2015 | 054 - Dec 2015/Jan 2016

2014

033 - February 2014 | 034 - March 2014 | 035 - April 2014

036 - May 2014 | 037 - June 2014 | 038 - July 2014

039 - August 2014 | 040 - September 2014 | 041 - October 2014

042 - November 2014 | 043 - Dec 2014/Jan 2015

2013

022 - February 2013 | 023 - March 2013 | 024 - April 2013

025 - May 2013 | 026 - June 2013 | 027 - July 2013

028 - August 2013 | 029 - September 2013 | 030 - October 2013

031 - November 2013 | 032 - Dec 2013/Jan 2014

2012

010 - Dec 2011/Jan 2012 | 011 - February 2012 | 012 - March 2012

013 - April 2012 | 014 - May 2012 | 015 - June 2012

016 - July 2012 | 017 - August 2012 | 018 - September 2012

019 - October 2012 | 020 - November 2012 | 021 - December 2012

2011

001 - March 2011 | 002 - April 2011 | 003 - May 2011

004 - June 2011 | 005 - July 2011 | 006 - August 2011

007 - September 2011 | 008 - October 2011 | 009 - November 2011

« Back to Home Page

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New project ready to tackle mitochondrial disease diagnosis dilemma

(L-R) : Professor John Christodoulou, Professor David Thorburn , AMDF CEO Sean Murray

Diagnosing mitochondrial disease (mito) is challenging. The disease manifestations are broad, the diagnostic pathway isn't standardised, and diagnostic tests are often invasive. Genetic testing is accurate and less invasive, but it has been mostly uncoordinated leading to inefficient diagnosis and unnecessary costs. The good news is a research project about to kick off in Australia is looking to change all of this.

The Mitochondrial Disorders Flagship, involving RCPA Fellows Professors John Christodoulou[1] and David Thorburn[2], is a collaboration between the Australian Genomics Health Alliance (AHGA) and the Australian Mitochondrial Disease Foundation (AMDF). The project is looking for the most effective way to diagnose mito by:

- comparing the effectiveness and benefits of genomic testing to those of current testing methods
- determining if genomic testing is a cost effective diagnostic tool
- addressing issues that have plagued genomic testing for mito in Australia.

"Patients identified as fitting into the probable or definite mitochondrial disease brackets will be offered next generation sequencing," explains Prof Christodoulou.

"Of these, half will be stratified to a combination of Whole Exome Sequencing and

mitochondrial DNA sequencing, and the other half will be stratified to Whole Genome Sequencing, to compare these diagnostic methods for mito patients."

AMDF CEO Sean Murray says mitochondrial disease lends itself to genetic testing because there are hundreds of genetic variations that cause the disease, it has a strong familial component, and it can follow any pattern of inheritance.

"AMDF got on board with this project because diagnosis is a critical issue for people with mitochondrial disease. A huge number of patients have clinical symptoms but no definitive diagnosis, and many patients undergo a difficult diagnostic odyssey. They have often seen multiple specialists seeking answers because mitochondrial disease can affect any organ and often masquerades as other diseases," he explained.

Prof Christodoulou says the Mitochondrial Disorders Flagship will operate through a clinical network of specialists in every state and territory of Australia who have experience with paediatric or adult onset mitochondrial disease. He is confident of success based on similar models in other areas that recorded positive outcomes, such as the Melbourne Genomics Health Alliance Demonstration Project for Childhood Syndromes.

"We are hoping to help patients avoid the traditional invasive diagnostic pathway for mitochondrial disease. This usually involves a muscle biopsy and MRI scan under a general anaesthetic which increases the risk of complications for patients with mito, especially for children," he explained.

Mr Murray said the trial addresses key needs in the mito community by improving the diagnostic process, supporting a community that often flies under the radar, and addressing the potential underdiagnosis of this condition.

The Mitochondrial Disorders Flagship is expected to run for two years and recruit about 200 patients. Prof Christodoulou says the results will be shared with the project's clinical networks, and based on its health economics data, an application could be submitted to the Medical Services Advisory Committee for a Medicare rebate for genomic testing for mitochondrial disorders.

"Earlier diagnosis of mitochondrial disease has many benefits including ending a patient's diagnostic odyssey, providing access to management pathways to alter disease progression, helping patients access support and plan for the future, and enabling young adult patients to make informed decisions about their reproductive options in the future" explained Mr Murray.

"We are expecting this project to have a very big impact for the mito community."

Mitochondrial Disease Fact File

- Mitochondrial disease can affect any organ, with any symptom, at any age.
- It reduces the ability of the mitochondria (cell power houses that produce 90% of the energy needed to sustain life) to produce energy.
- Mitochondrial disease can result in whole organ failure and potentially death.
- 1 in 200 Australians carry the genetic mutations that put them at risk of developing mitochondrial disease.
- Mitochondrial disorders are the most common inherited metabolic diseases. They affect more than one in 5000 births and encompass more than 250 disease genes.

[1] Professor Christodoulou is the Chair of Genomic Medicine at Murdoch Children's Research Institute & The University of Melbourne co-lead of the Mitochondrial Disease Flagship with Professor Thorburn.

[2] Professor Thorburn is the Head of Mitochondrial Research at the Murdoch Children's Research Institute.

Mitochondrial Disease was covered in the September 2013 edition of ePathWay.

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« Back to Home Page

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How do you define a pathologist?

Delivering a plenary lecture about what a pathologist's role is, to a room full of pathologists, at a pathology conference, might seem odd. Yet when Professor Jennifer Hunt did exactly this, she held her audience spellbound.

Before we report on Prof Hunt's talk, these 'definitions' are testimony to the difficulty of defining and understanding the role of a pathologist.

- *'A doctor who has expert knowledge of pathology' – Cambridge Academic Content Dictionary.*
- *A specialist in pathology specifically: one who interprets and diagnoses the changes caused by disease in tissues and body fluids - Merriam-Webster.*
- *A physician who identifies diseases and conditions by studying abnormal cells and 'tissues' - MedicineNet.com.*
- *A scientist who studies the causes and effects of diseases, especially one who examines laboratory samples of body tissue for diagnostic or forensic purposes - Oxford Dictionary.*
- *An expert in the study of diseases, especially someone who examines a dead person's body and cuts it open to discover how they died – Cambridge Advanced Learner's Dictionary and Thesaurus.*

Pathologists are actually all of the above - doctors, specialists, physicians, scientists and

experts in the study of diseases - so Prof Hunt addressed what they are not.

“We are not ‘the lab’, we are not working behind the paraffin curtain, and we are not the doctor’s doctor,” she explained to her colleagues.

“We are our patient’s doctor from before birth to after death, and usually the only one they don’t meet. Yet I’m sure we can all think of a patient in the past week that we feel connected to, because I know I can.”

Prof Hunt also tagged pathologists as innovators, early adopters, translators of science into medicine, and indispensible.

Professor Jennifer Hunt

“The experiment has been done in terms of what a hospital without pathologists looks like. During the Haiti disaster, the University of Miami Tent Hospital remembered to bring operating rooms, surgical equipment, nurses and surgeons, but they forgot to bring pathologists and a laboratory,” she explained.

“They very quickly discovered that they couldn’t treat their patients without a pathologist to diagnose and inform their treatment decisions such as does this patient need antibiotics and if so, which one, and is this a tumour or an injury on this patient. There were consequently emergency calls to bring pathologists and laboratory equipment to them ASAP so they could accurately diagnose and effectively treat their patients.”

Prof Hunt said she shows the RCPA’s If Pathologists Didn’t Exist video series to her medical students to demonstrate the indispensible role of pathologists.

“We are also the doctors who will stake out the limits of the knowable. Advances in medicine that happened on our watch that have revolutionised patient care include personalised medicine, precision diagnostics, companion diagnostics, molecular profiling, targeted therapy and germline genetic testing. We are also responsible for embedding these innovations into medicine.”

While these advances are extremely significant and have changed the landscape of medicine, there is no time for resting on the profession’s collective laurels.

“There are still many challenges ahead including managing the incredible burden of health information, major investment in individual and population research in genotype-phenotype, the essential involvement of the patient and family, and entirely new training for healthcare providers.”

When you consider the scope of a pathologist’s skill set, and the changing medical landscape they are transforming and then navigating, defining a pathologist is challenging. We’ll therefore defer to Prof Hunt’s definition, and the title of her talk, which is: Every patient’s doctor from before birth to after death: The indispensable pathologist.

Professor Jennifer Hunt is Aubrey J. Hough Jr, MD, Endowed Professor of Pathology and the Chair of Pathology and Laboratory Medicine at the University of Arkansas for Medical Sciences. She delivered the Eva Raik Plenary at Pathology Update in Sydney.

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« Back to Home Page

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Newborn screening is navigating uncharted frontiers

Newborn screening (NBS) is a public health success, but it is facing challenges created by rapid technological advances that have identified many new candidate disorders that might fulfil criteria for screening. The issues that accompany genetic testing also mean NBS is navigating uncharted frontiers.

Professor Bridget Wilcken AM, Senior Staff Physician at the Genetic Metabolic Service at Sydney Children's Hospital Randwick, says issues being dealt with include:

- Choosing which disorders to test for.
- Screening 'because we can'.
- Being able to estimate benefits and harms realistically.
- Over-diagnosis.

"There is also a growing possibility that next-generation sequencing can be efficiently applied to newborn screening. Screening programs must be efficient and avoid harm, so there must also be a strategy in place to deal with the large numbers of incidental findings and variations of unknown significance that would accompany this process."

Prof Wilcken said some major challenges in incorporating next-generation technologies into NBS include:

- What conditions to test for. “For example, do we add significant adult-onset conditions or untreatable conditions, and will consent be required?”
- Is there a will to change the general aims of NBS. “For example, should NBS benefit the newborn during infancy or in later life, or the newborn and/or the family, or should it benefit the population?”
- What findings should be reported to parents?
- Should some data not be reported but stored for use in later life?
- How do we deal with incidental findings and variants of unknown significance?

“Next generation sequencing is here to stay, but more information means much more is discovered about individual genes over time. This therefore means that interpretation of results will remain difficult and contentious for some time,” explained Prof Wilcken.

“It is also unclear if next generation sequencing can completely replace current functional tests, as the comparative cost is still extremely high. It may be a test that happens after the initial NBS tests (called second-tier testing), but one thing is certain. We will be discovering and ‘inventing’ many new disorders.”

NBS using filter-paper blood samples has existed for over 50 years. How it will evolve over the next 50 years is difficult to predict, although Prof Wilcken has one prediction of her own (modified from Aldous Huxley).

“Newborn screening is making such tremendous progress that, if we are not careful, there will hardly be a healthy baby left.”

Professor Wilcken delivered the talk *Controversies in neonatal screening* at Pathology Update in Sydney.

More information about NBS can be found here.

« Back to Home Page

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Pathology results need context to detect deterioration in a patient's condition

When it comes to detecting or monitoring the deterioration in a patient's condition, the pathology result is just one piece of information in the whole clinical picture. For example, a 'normal' test result for one person can be a sign of deterioration for another, and that's why clinical context matters.

Dr Penny Coates, Clinical Director of Chemical Pathology at SA Pathology, says requesting a barrage of investigations is rarely helpful, because signs that a patient's condition is deteriorating probably won't leap out from the page.

"Pathology results must be interpreted within the clinical context alongside other clinical observations and investigations. They are not meant to be read in isolation. I tell my registrars and juniour doctors not to go on random fishing expeditions when requesting pathology tests. Instead, frame the tests as questions such as 'Does this patient have this issue?' and go from there. That way they are setting up investigative and diagnostic pathways," she explained.

Another reason pathology results may not flag a patient's deteriorating condition on their own is the test's reference parameters.

"Some disease processes can be quite advanced before some pathology tests flag a problem. For example, the liver can lose up to three quarters of its function before a liver

function test returns an abnormal result. Once again, this test is only one piece of the overall clinical picture and must therefore not be used as the only indicator of disease."

One place where signs of patient deterioration are monitored closely is in an intensive care unit, and even then it's not all black and white.

"There is a lot going on in these units, and when people are that sick some pathology results are not very useful in determining if a patient's condition is improving or deteriorating if the clinical context is not considered," Dr Coates said.

"For example, a pathology test result may be accepted as normal when it is within 10% to either side of a reference value, but just a five per cent change in the result of that test may indicate a significant change in the patient's condition. This is where the test result requires interpretation by a pathologist to identify what is a significant change in a result for that patient based on their clinical condition."

Signs of deterioration can be masked by other factors as well. Dr Coates says a pathology test can return an inaccurate result when:

- The wrong test is requested and it therefore doesn't return a meaningful result for that patient's condition.
- There is interference in the test sample. For example, a haemolysed blood sample (where the red cells are damaged and their contents are released into the plasma) can cause a very high plasma potassium concentration to be measured, when the patient's potassium isn't elevated at all.
- Drugs can also interfere with test results. For example, some medicines can cause a high creatinine level to be measured, when it isn't elevated at all.
- The patient's biochemistry interferes with the test result. For example, heterophile antibodies may affect a number of laboratory tests resulting in false elevation of tumour markers, endocrine tests, cardiac injury markers and drug levels.

"Pathology tests are only part of the puzzle. The whole clinical picture must be considered, and when this happens, the likelihood that pathology tests detect or flag a patient's deteriorating condition also increases," says Dr Coates.

« Back to Home Page

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