ePathWay
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

JULY 2019 | PUBLISHED BY RCPA ISSUE #093

IN THIS ISSUE

INTERESTING FACTS

5 years

the duration of the RCPA's training program to become a genetic pathologist

1,650

the number of deaths caused by Ebola Virus Disease in the Democratic Republic of Congo since August 2018[1]

6.5%

HbA1c levels of 6.5% or higher are seen in asymptomatic individuals with type 2 diabetes mellitus.[2][3]

Welcome to the July issue of ePathWay

ePathway is an e-magazine designed for anyone interested in their health and wellbeing and the integral role pathology plays in the diagnosis, treatment and management of diseases.

This month's issue of *ePathway* looks at the following:

- The need to identify haemoglobinopathies when using HbA1c as a diagnostic test
- Ebola Virus Disease; a closer look
- An insight into genetic pathology training
- Increased Impact Factor for RCPA journal, *Pathology*

With health authorities in the Democratic Republic of Congo struggling to contain a deadly outbreak of Ebola Virus Disease (EVD), we spoke with Doctor Mike Catton, Deputy Director at The Peter Doherty Institute for Infection and Immunity in Melbourne to learn more about this rare but severe, often fatal illness in humans. Along with other public health measures, efforts to develop an effective vaccine against Ebola virus disease (EVD) must continue.

The HbA1c test is useful in both diagnosis and monitoring the quality of glucose control in diabetes, and also assists in making treatment decisions such as adjusting insulin doses. However, there remains some debate regarding its applicability for diagnosis and, with its adoption as a diagnostic test, accurate results are vitally important and awareness of possible confounding factors such as haemoglobin variants has increased. We spoke with Associate Professor Chris Florkowski to discuss the cautions and caveats regarding using HbA1c as a diagnostic test.

Recently released 2018 reports show that the impact factor for Pathology, the official journal of the Royal College of Pathologists of Australasia (RCPA) has increased to 3.163, marking the second consecutive year that the journal has received an impact factor over three. We spoke to Pathology Editor, Prof Delahunt to discover what an impact factor is and why Pathology has seen a dramatic annual upwards trend.

Genetic pathology is one of the newest disciplines in pathology, with genetics rapidly becoming the basis of almost every disorder. The Royal

College of Pathologists of Australasia runs a 5-year training program in genetic pathology, a discipline which involves the diagnosis of genetic diseases primarily by overseeing the testing of patient samples for mutations in DNA or RNA. We spoke with recent graduate Doctor Cheng Yee Nixon to discuss more about this exciting discipline, and also what is involved in the training process.

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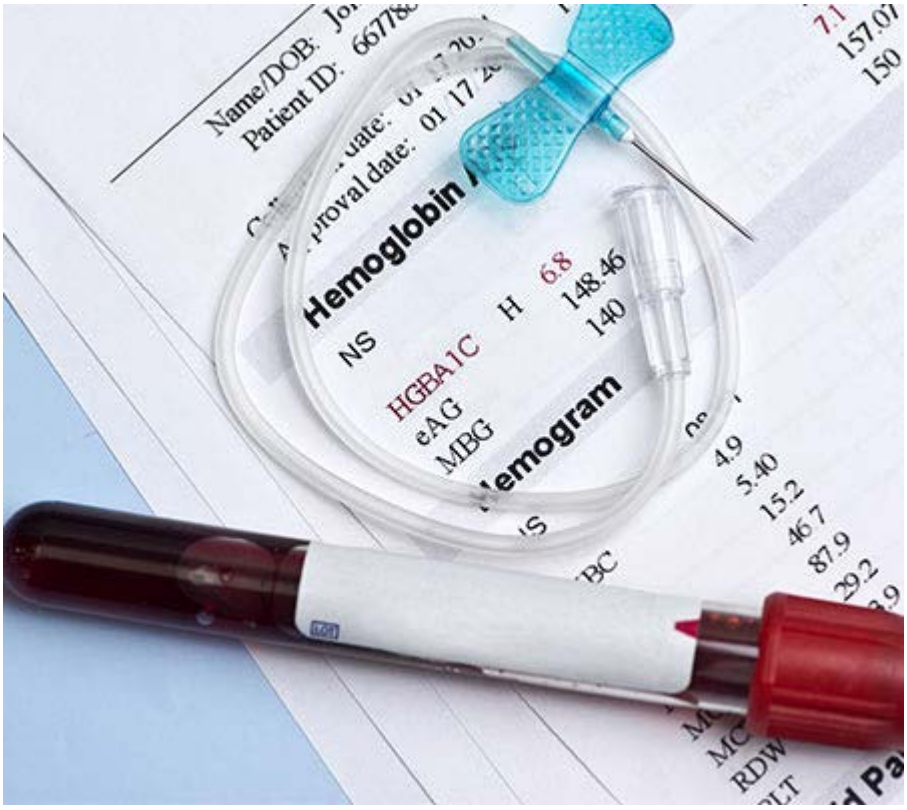
The need to identify haemoglobinopathies when using HbA1c as a diagnostic test



The Haemoglobin A1c (HbA1c) test is a blood test which is commonly used to help diagnose and monitor people with diabetes. Although the test is formally endorsed in many countries as a form of diagnosing and monitoring type 2 diabetes, there remains some debate regarding its applicability for diagnosis. We spoke with Associate Professor Chris Florkowski to discuss the cautions and caveats regarding using HbA1c as a diagnostic test.

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Ebola Virus Disease; a closer look

3.163

The current impact factor for Pathology, the official journal of the RCPA[4]

Source:

[1] https://www.who.int/news-room/detail/15-07-2019-high-level-meeting-on-the-ebola-outbreak-in-the-democratic-republic-of-the-congo-affirms-support-for-government-led-response-and-un-system-wide-approach

[2] https://www.webmd.com/diabetes/guide/glycated-hemoglobin-test-hba1c

[3] https://www.ncbi.nlm.nih.gov/pubmed/26175248

[4] https://www.journals.elsevier.com/pathology

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On 17 July 2019, the WHO declared the ebola virus disease (EVD) outbreak in the Democratic Republic of Congo a public health emergency of international concern. With health authorities struggling to contain the country's deadly outbreak where more than 1,650 people have died since it began nearly one year ago, we spoke with Doctor Mike Catton, Deputy Director at The Peter Doherty Institute for Infection and Immunity in Melbourne to learn more about this severe, and often fatal, haemorrhagic disease.

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An insight into genetic pathology training

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Increased impact factor for RCPA journal, *Pathology*

The impact factor is the most widely used tool for measuring the importance or rank of a journal. The higher the impact factor, the more highly ranked the journal. Recently released 2018 reports show that the impact factor for Pathology, the official journal of the Royal College of

Professor Brett Delahunt

Pathologists of Australasia (RCPA) has increased to 3.163. Pathology Editor, Prof Delahunt has thanked the Pathology Editorial Board, reviewers, authors and readers who continue to support the journal and contribute to its international success.

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The need to identify haemoglobinopathies when using HbA1c as a diagnostic test

The Haemoglobin A1c (HbA1c) test is a blood test which is commonly used to help diagnose and monitor people with diabetes. Although the test is formally endorsed in many countries as a form of diagnosing and monitoring type 2 diabetes, there remains some debate regarding its applicability for diagnosis.[1] We spoke with Associate Professor Chris Florkowski to discuss the cautions and caveats regarding using HbA1c as a diagnostic test.

“Haemoglobin is the protein in red blood cells which carries oxygen throughout your body. HbA1c is the term used to describe haemoglobin which is joined together with glucose, specifically at one particular site; the N-terminal valine of the beta chain. HbA1c gives a measure of what the average blood glucose level has been in the previous 2-3 months, reflecting the life span of the red blood cell,” said A/Prof Florkowski.

The HbA1c test is useful in both diagnosis and monitoring the quality of glucose control in diabetes, and also assists in making treatment decisions such as adjusting insulin doses. For those people without diabetes, normal HbA1c is between 4% and 5.6%. HbA1c levels of 6.5% or higher are seen in those people with diabetes.[2]

“HbA1C testing offers a number of advantages over other diagnostic tests for type 2 diabetes such as a glucose test. The HbA1c test is a single blood test which does not require any particular preparation such as fasting, which is required prior to a glucose test or an oral glucose tolerance test, which has until recently been the preferred way of diagnosing diabetes. HbA1c also gives a stable reading and is not subject to the short-term variations that are seen with blood glucose. The diagnostic cut-offs relate to clinical

outcomes, namely the risk of developing complications," said A/Prof Florkowski.

Laboratory methods for HbA1c are accurate and precise. In Australia, a HbA1c level of 48 mmol/mol (6.5%) is endorsed as the cut-off for diagnosing diabetes in asymptomatic individuals at high risk of diabetes. In New Zealand, the adoption of HbA1c as a diagnostic test was coordinated with the adoption of exclusively molar units with the higher diagnostic cut-off rounded up to ≥50 mmol/mol (≥6.7%), and with repeat testing on a second occasion in individuals without symptoms.

"In New Zealand, part of the rationale for the rounded cut-off for HbA1c was to make the molar units more memorable, although also to maximise the specificity for the diagnosis of diabetes. It may be argued that some cases of diabetes (maybe 20-30%) will be 'missed' by using a higher cut-off, although such individuals will usually have HbA1c close to the cut-off (41–49 mmol/mol), will be re-tested in 6–12 months and enter a lifestyle programme," said A/Prof Florkowski.

In conditions where the life span of the red blood cell is shortened, such as in regular blood donors, the HbA1c will be lowered and therefore will not accurately reflect underlying glucose control. HbA1c can also be confounded by the presence of haemoglobin variants due to their effects on red cell survival and/or analytical interference with the laboratory method. In these cases, a HbA1c test may also reveal haemoglobinopathies. Dr Helen Moore, haematologist at Waikato District Health Board, explains that further tests may be required if haemoglobinopathy is suspected.

"Haemoglobinopathy encompasses all genetic diseases of haemoglobin and is among the most common inherited diseases in the world. The condition falls into two main groups; thalassemia syndromes and structural haemoglobin variants, however the terms are often used interchangeably. We often pick up haemoglobinopathies incidentally, for example in young women who may not have had a Complete Blood Count (CBC) done before, we may pick them up during pregnancy."

"A HbA1c test will often pick up an abnormal haemoglobin peak, however it won't tell you what it is. What we would do then is look at the patient's ethnicity, look at their blood parameters and then, particularly if they are pregnant, we would then do a haemoglobinopathy screen to try and determine if this is something that is significant or not," said Dr Moore.

Patients may be known to have a haemoglobin variant. The laboratory may suspect a haemoglobin variant by detecting an abnormal chromatogram when measuring HbA1c by certain methods or clinicians may suspect a variant through results that are discordantly high or low compared with prevailing blood glucose results. In these situations, the laboratory can investigate further with haemoglobin electrophoresis, mass spectrometry or DNA based diagnostic tests. In many situations, however a variant may be present without any significant effect on the HbA1c result.

Increasingly, with the adoption of HbA1c as a diagnostic test, accurate results are vitally important and awareness of possible confounding factors such as haemoglobin variants has increased. Hence the recognition of such variants appears to be gaining in pace.

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[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3799221/

[2] https://www.webmd.com/diabetes/guide/glycated-hemoglobin-test-hba1c

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Ebola Virus Disease; a closer look

On 17 July 2019, the WHO declared the ebola virus disease (EVD) outbreak in the Democratic Republic of Congo a public health emergency of international concern [1]. With health authorities struggling to contain the country's deadly outbreak where more than 1,650 people have died since it began nearly one year ago [2], we spoke with Doctor Mike Catton, Deputy Director at The Peter Doherty Institute for Infection and Immunity in Melbourne to learn more about this severe, and often fatal, haemorrhagic disease.

"EVD is a rare but severe, often fatal illness in humans. Popular media often use 'ebola' interchangeably, referring to both a disease and a virus. However, EVD is caused by ebola viruses, of which there are five species. Since 1976 when ebola viruses were first discovered, human outbreaks have been caused by two of these species: Zaire ebola virus and Sudan ebola virus, and have occurred in sub-Saharan Africa. There have never been cases of EVD in Australasia.

"It is understood that ebola viruses are ancient viruses which have infected mammals such as bats for millions of years. Occasionally ebola virus spreads into larger animals such as primates, and from time to time there is onward spread into humans which may then cause outbreaks. It is spread in the human population through human-to-human transmission. Overall death rates are about 50% for Sudan EVD, and 80% for Zaire EVD."

EVD is not an airborne infection, it is transmitted in humans though close and direct contact with infected bodily fluids, the most infectious being blood, faeces and vomit. It can also be transmitted indirectly, via contact with previously contaminated surfaces and objects, however this risk is low. The incubation period for EVD is from 2 to 21 days, and a person infected with ebola cannot spread the disease until they develop symptoms. [3]

“Ebola disease tends to go through three phases. The onset of symptoms is sudden, but for the first few days these are non-specific symptoms of high fever, weakness, lethargy and muscle aches. This is followed by about a week of gastrointestinal symptoms such as nausea, vomiting and diarrhoea, which can be mild or severe. The survivors begin to recover at this point, but many patients progress to shock and failure of multiple organs. Uncommonly, abnormal bleeding such as gastrointestinal bleeding, haemorrhages in the eye, oral bleeding or leakage of blood into the skin can feature at this stage. However, this bleeding is more common in the movies than in real life. Death is common amongst patients that progress to shock,” said Dr Catton.

EVD is often difficult to clinically distinguish from other infectious diseases such as malaria, typhoid fever and meningitis. There are a number of diagnostic methods to confirm that symptoms are caused by Ebola virus infection, and it is strongly recommended that diagnostic tests which have undergone an independent and international evaluation be considered for use. [4]

“These days, molecular testing for ebola virus genetic material is done using blood samples or swabs. This is called real-time polymerase chain reaction (RT-PCR) and is the standard testing approach for EVD. It is very accurate, very quick, taking only a few hours, and can be done even in quite spartan field laboratories set up at the site of outbreaks in Africa. Biocontainment laboratory facilities and/or equipment is used to keep the scientist safe during this step.

“Amplifying and detecting the ebola virus gene target from this genetic material is done on automated RT-PCR analysers and the results are visually displayed with computer software. The RT-PCR analysers can be made relatively small and portable, which allows for field use,” said Dr Catton.

There is still no fully validated treatment or vaccine for EVD, however early supportive care, with rehydration with oral and intravenous fluids and symptomatic treatment, improves survival. However, there have been exciting advances in recent years in terms of treatment for EVD including blood treatments, immune therapies and drug therapies.

“Early data on the effectiveness of some experimental antiviral drugs, and of cocktails of synthetic antibodies in treating EVD have shown promising results. There is also promising data on experimental ebola virus vaccines, and these have been used in field trials during recent outbreaks,” said Dr Catton.

Since the outbreak of EVD was declared in DRC in August 2018, a ring vaccination strategy has been implemented in North Kivu and Ituri provinces. In May 2019, the WHO reported that, since the outbreak began, more than 111,000 people in DRC have been vaccinated with an experimental vaccine called rVSV-ZEBOV-GP. [5]

The unlicensed rVSV-ZEBOV-GP vaccine consists of an animal virus called vesicular stomatitis virus (VSV), which has been genetically engineered to contain a protein from the Zaire ebola virus, and therefore provokes an immune response to the ebola virus. Preliminary results released by the WHO confirm high efficacy of the vaccine against ebola, and a reduction in overall case fatality rates. [6]

Despite this encouraging early data on rVSV-ZEBOV-GP, the outbreak of EVD in DRC has worsened recently due to violent attacks against aid workers and a communication break down between communities and response workers. In May 2019, the WHO’s Strategic Advisory Group of Experts released new guidelines to address these concerns.

The threat of an EVD outbreak in Australia is low. If a traveller has recently returned from a trip to an ebola virus high risk area, and presents either at the border, or to their doctor with symptoms consistent with EVD, then they are likely to be tested for the disease by an expert public health laboratory using RT-PCR.

Testing can be done accurately and fast in Australia. The national reference laboratory for African haemorrhagic fevers like EVD is the Doherty Institute, Melbourne. At this laboratory, testing is available around the clock, or support will be provided to the local laboratory as required.

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[1] https://www.who.int/news-room/detail/17-07-2019-ebola-outbreak-in-the-democratic-republic-of-the-congo-declared-a-public-health-emergency-of-international-concern

[2] https://www.who.int/news-room/detail/15-07-2019-high-level-meeting-on-the-ebola-outbreak-in-the-democratic-republic-of-the-congo-affirms-support-for-government-led-response-and-un-system-wide-approach

[3],[4] https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease

[5] https://www.who.int/news-room/detail/07-05-2019-who-adapts-ebola-vaccination-strategy-in-the-democratic-republic-of-the-congo-to-account-for-insecurity-and-community-feedback

[6] https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf

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An insight into genetic pathology training

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“There's a saying that was bandied about when I was in medical school: 'There is a niche for everyone in medicine'. I never used to believe it. While everyone at med school had multiple things they were interested in, I just couldn't find the one thing I wanted to do for the rest of my life. Having said that, I have always been interested in genetics, but I (a) didn't really know that genetic pathology was an option (no one ever talked about it - not at career nights or anything!), (b) had never met a genetic pathologist, ever (turns out there were none in NZ, so not really anything I could do about that!), and (c) never thought I'd be smart enough to do genetics. As evidence of just how little is known about genetic pathology, people often assume I do one of 4 things: look down a microscope, help people find their ancestral roots, do crime scene stuff like in CSI, or do 'research'. So, I think it's fair to say that it isn't a well-known specialty, even among medics.

“No one in my family is a pathologist. In fact, no one in my immediate family is in medicine. My mum still asks me what I do, and struggles to pronounce pathology! Genetic pathology appeared at a crossroads in my life and ‘chose me’. In a strange and unexpected turn of circumstances, I found myself interviewing for a role that I had dismissed three years before as being too clever for me, turning instead to general surgery when I was offered a place on the training programme. This three-year detour did feel a touch slow, however, the beauty of genetic pathology is that everyone has

their own story, their own journey, which makes for a combined wealth of experience and knowledge.

“Genetics has rapidly become the basis of almost every disorder, even though we don't fully understand it just yet. It wasn't that long ago that we could only diagnose genetic disorders by phenotype and symptoms - now we can look at a person's entire genetic code and find that single error underlying their condition, even without knowing beforehand what we are looking for, and in a matter of days! It's really quite incredible. It’s also not just in diagnosing conditions, but also in deciding appropriate treatment, monitoring response, providing families with reproductive risk information and so much more. Genetic pathology can impact all life stages - from a five-day old blastocyst undergoing genetic screening to see if it will become a viable embryo, to an older woman with cancer who is undergoing testing to see if she is expected to be responsive to a particular drug. It's constantly changing and improving, and certainly keeps you on your toes!

“In terms of training, once you complete medical school, you spend at least two years as a house officer in order to get a broad working view of the various medical and surgical specialties. You can then become a registrar (a more specialised doctor, training in your field of interest). Interestingly, most of us genetic pathologists started out life in other specialties - paediatrics, obstetrics and gynaecology, general medicine, general surgery, even general practice before seeing the light. I think our backgrounds in these areas help shape our practice and our ability to interpret complex data in a manner that is relevant to our colleagues.

“Five years is spent training in genetic pathology, and at least one of those years needs to be spent in a different lab. This is not much of a problem in cities such as Sydney, as there are multiple labs to train at. However, in places like New Zealand, where there are only two genetic labs in the country to train, or in Perth and Adelaide where there is only a single genetic lab, this is a big deal. It means uprooting family and life to start anew in a different place! I moved from Christchurch to Sydney for 15 months with my husband and dog, leaving his two teenage boys behind with their mother as they were settled at school. My husband flew back every month for a week each time, and the boys had the opportunity to come over in school holidays. It was an unusual time, but well-worth the experience gained. I got to analyse big genomic data (whole exome data), which I didn't have access to in Christchurch, and was able to bring back to New Zealand the knowledge and skills I gained when I came back as a brand new pathologist.

“Training in genetic pathology involves learning about a lot of things that they don't teach you anywhere else, not in medical school or on the wards. You first of all learn the various genetic tests and assays that your lab offers - how to perform them, why they are used, how to interpret results, how to write intelligent reports - gaining a good grounding in techniques and the underlying biology of the disorders. You learn how to ensure quality of the test and result, how to think about whether or not a test has any clinical utility, how to answer the clinical question posed, and what the ethical implications are for the testing we do. You learn how to decode 'genetics-speak' for other clinicians, how to educate and advise other clinicians, how to manage your scientists, how to provide direction. You learn that it takes a team to do this job well. And although you never see patients, they are always at the forefront of what you do, and the reason why we strive to do it right.

“What I find exciting about the future of genetic pathology is the endless possibilities of genomic technology, however this must be coupled with responsibility and accountability for all those using it, especially in the diagnostic setting. Whole exome sequencing in a child today could be used in a fetus tomorrow, and in fetal DNA floating in mum's blood next week. Technology is constantly pushing the boundaries of what is possible, and it is up to us to help shape and regulate what is acceptable. It is also becoming increasingly clear that we can't (and shouldn't!) do this alone. Working together across different centres, sharing data, resources and skills is the only way we will be able to advance knowledge in this field. I’m also excited that perhaps someday, there might be more than two genetic pathologists here in NZ, and that we might have our own job category in the Medical Council's list of professions (instead of being Pathologist>Other)!

“I think all of medicine is important, and that we can't do anything without each other. However, I do think the value of pathology is under-recognised, simply because we are not the face the public sees - or even the face that the other clinicians see! And yet, how often do we rely on pathology to help rule in or rule out a diagnosis? Pathology is not that thing that they do in that building over there, taking blood, feeding it into a machine, and pulling out a bit of paper with the result... it is the very core of what we do in medicine. Medicine IS pathology, and we'd be pretty useless without it!”

For information regarding vacancies or when training positions will become available, please contact geneticpathologytraining@gmail.com

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Professor Delahunt said,

“The impact factor is a measure of the average frequency with which articles published in two consecutive years in a journal have been cited in the following year. It is the ratio between citations and recent citable items published, and it is the one tool that can be used to compare journals in a subject category. A high impact factor means that a journal is more highly ranked and therefore deemed to be more important than those with lower ones.

“You cannot predict an impact factor as it is dependent on the quality of articles published within a journal each year. In general, we have seen a dramatic upwards trend of the impact factor for *Pathology* annually and this is the second consecutive year that the journal has had an impact factor over three, which is quite an achievement for a general pathology journal. This is largely due to the fact that *Pathology* has a policy to only accept high quality articles. We also have a strong international editorial board which helps us to attract good papers.”

Clarivate Analytics, formerly The Institute for Scientific Information (ISI), is responsible

for publishing the Journal Citation Reports which provide quantitative tools for ranking, evaluating, categorising, and comparing journals.

“Opinions vary widely as to what constitutes a good impact factor. However, it seems to be the case that an impact factor of three is the watershed. You will also find that some funding organisations have a requirement that applicants have been published in journals with an impact factor of three. This is certainly something that we have noticed, and we have received a lot more submissions since *Pathology* hit an impact factor of three for the first time last year.

“Success breeds success and, in general, we are finding that the number of submissions for *Pathology* is increasing each year. For example, in 2009 we received 264 articles for consideration, and in 2018 this had increased to 419. However, it is also important to note that we receive a wide range of both good and bad articles, and although the submission rate has increased, the rejection rate has also gone up significantly,” said Prof Delahunt.

Pathology is the official journal of the RCPA and is committed to publishing peer-reviewed, original articles related to the science of pathology in its broadest sense, including anatomical pathology, chemical pathology and biochemistry, cytopathology, experimental pathology, forensic pathology and morbid anatomy, genetics, haematology, immunology and immunopathology, microbiology and molecular pathology. The journal has specific instructions and guidelines for submitting articles and acceptance of a contribution is conditional upon the work described being original.

“The impact factor is just one measure of the importance of a journal and unfortunately it can be manipulated. For example, you can cite yourself, but that’s something that we do not encourage. In addition to accepting only high quality articles, what we try to do is to make sure that the articles that are published in *Pathology* have utility to reporting pathologists, this means that in addition to attracting citations, good articles assist pathologists in their every day practice,” said Prof Delahunt.

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