



PathWay

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA



Issue #006

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- Prostate cancer: It's about using the best tools effectively
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Welcome to the August edition of ePathWay

This month's articles include a look at the blood test for prostate cancer, the international project that is mapping the genetic sequence of 50 of the most common types of cancers, and a pathologists' perspective on cholesterol and haemochromatosis.

In fact, pathologists offer an interpretive perspective that is quite unique when it comes to looking at diseases. They often work at the cellular level which is why they are important team members in the project that is mapping the genetic sequences of cancers. This article also recognises August's focus on genetic research thanks to 'Jeans for Genes' day.

We welcome your feedback about the stories covered in ePathWay, and hope you find it an invaluable way of being kept up to date about pathology in Australasia.

Interesting Facts

1 in 300

The estimated number of people with the genetic disease Haemochromatosis

12 percent

The estimated number of Australians who are carriers of the Haemochromatosis (HFE) gene

Iron overload is usually a family affair

1 in 4

The risk of inheriting
Haemochromatosis when both parents
are carriers

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International consortium is uncovering cancer's hidden secrets

Cancer. It's a heart-stopping word capable of turning lives upside down. It has also kept its secrets to itself – until now. An internationally coordinated effort to map the unique genetic sequence of cancers may be the key to finally defeating one of medicine's toughest opponents.



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Controversy surrounding the PSA blood test for early, potentially curable prostate cancer has left men confused about what they should do. The findings from large clinical trials have not revealed a clear answer, with one study showing no effect and another up to a 40 percent reduction in death from prostate cancer. In the interim, most medical professionals agree that men should be given up-to-date information about the potential benefits and risks of this test, based on the best available evidence, and the opportunity to weigh up the options with their doctors. If they decide to be tested, then the best available tools should be used including the PSA test for prostate cancer.

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Dave and Steve: A tale of two cholesterol levels

Meet Dave and Steve. Dave watches his weight carefully, exercises regularly, eats mostly fresh food and lean white meat, and uses healthy fats and oils when he cooks. His mate Steve loves to eat pies and chips with a beer, rarely exercises, doesn't know a good fat from a bad one, and hasn't caught sight of his toes for many years thanks to his generous 'beer belly'.

Dave and Steve are both 45 and they both have a normal cholesterol level. Steve thinks this means he doesn't have to change his lifestyle.



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Iron overload is usually a family affair



Bleeding people as a treatment seems almost medieval, yet it's the standard treatment for people with the genetic disease haemochromatosis. They absorb more iron from their diet than is required, and because the body cannot easily remove iron once it has been absorbed, the excess builds up in organs and joints causing iron overload.

"Haemochromatosis is a long slow clinical process that, for many people, has minimal associated symptoms, or alternatively non-specific symptoms such as progressive onset of tiredness as well as joint aches and pains," explains Dr David Ravine, medical geneticist at PathWest and University of Western Australia's School of Pathology and Laboratory Medicine. "It may take some time for the penny to drop, but if it's left untreated the clinical consequences can be severe including premature onset diabetes, heart disease, liver failure and cancer."

Iron is essential for the production of haemoglobin which carries oxygen to the tissues. According to Dr Alan McNeil, head of chemical pathology at Dorevitch Pathology, iron is also toxic to the body and must be carried around in the blood by an iron-binding glycoprotein called transferrin.

“Transferrin is normally about 30 percent loaded with iron, but in people with haemochromatosis it is usually loaded with 50 to 70 percent or more,” he says.

Pathologists test if a person has too much stored iron by measuring blood transferrin and iron levels, and then calculating the iron saturation level. Dr McNeil says if this level is high and the diagnosis of haemochromatosis is confirmed, then the treatment is simple.

“What people with haemochromatosis need to do is simply remove some blood, just like a blood donation. This stimulates the body to make more blood which uses up the excess iron,” he says. “If people have haemochromatosis, then their families should be screened for the disorder as well.”

Haemochromatosis is a recessive gene disorder meaning both parents must be carriers of the mutated HFE gene for the disorder to be passed on. Carriers inherit one HFE gene and one normal gene and are usually healthy. Haemochromatosis is also more common in people of Western European origin.

“The first HFE gene mutation probably occurred around 70 generations ago. It is now very common and occurs in more than 10 percent of some populations,” explains Dr Ravine. “Because of this it is suspected that carriers of an HFE mutation had some survival advantage, such as better protection from serious iron deficiency in times of famine, but we don’t really know.”

Both doctors stress that haemochromatosis is easily diagnosed and treated. The HFE mutation can also be traced through families with a simple blood test to identify other relatives who may unknowingly have iron overload. Early detection is important because iron levels build up slowly over time, and when clinical signs start emerging the damage to organs and joints is often already done.

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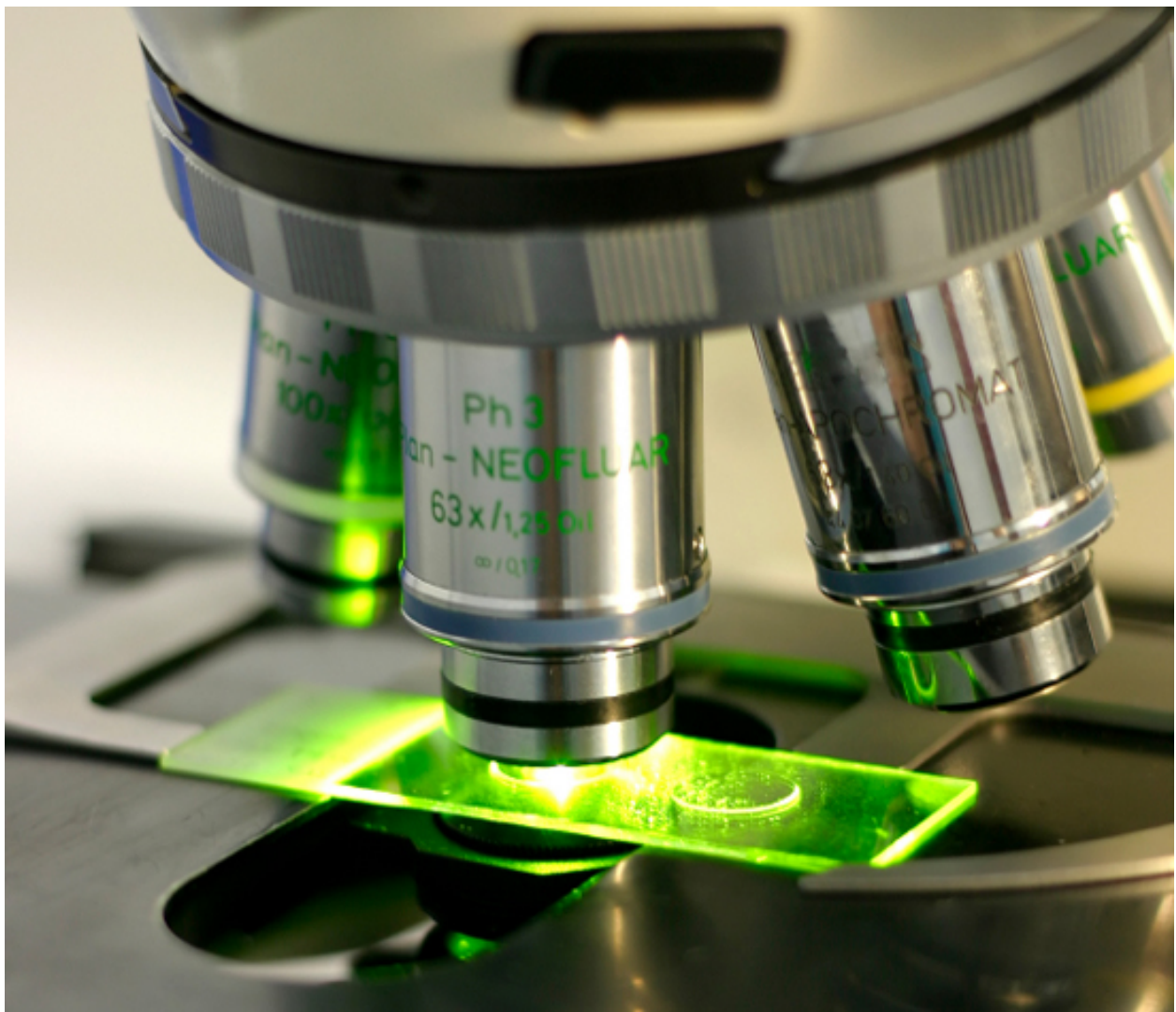
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"All cancer cells have a huge number of abnormalities and each cancer cell is genetically different. This can explain why someone may live for 12 months, and another person may live for three years,

when they both have the same type of cancer,” says Ms Amber Johns on behalf of The Australian Pancreatic Cancer Genome Initiative, which is under the umbrella of the International Cancer Genome Consortium (ICGC). “Cancer cells may look the same down a microscope, but they are all different at the genetic level.”

The ICGC is an international collaborative effort to map the genetic sequence of the 50 most common types of cancer. Results from each country are shared on a common database where the public can see summaries of the data, and researchers worldwide can access detailed reports.

The project’s aim is to accelerate research into the causes and control of cancer with Australian researchers, led by the Garvan Institute of Medical Research in Sydney and the University of Queensland’s Centre for Medical Genomics, planning to map the genetic sequences of 400 pancreatic cancers. So far 100 tumour sequences have been completed, and the most common and potentially important genetic mutations (faults) identified.

“From these first 100 tumour sequences we can begin to really work out what drivers are promoting cancer and what genes have been lost that would normally prevent cancer,” says Dr Anthony Gill from the Royal North Shore Hospital and visiting pathologist at the Garvan Institute. “By applying these genetic findings to treatment solutions, practical results for patients could be seen within two or three years.”

The results of this project could have huge ramifications for cancer patients worldwide. For example, Ms Johns says the survival rate from pancreatic cancer hasn’t changed for 40 years, so researching this type of cancer at the molecular level is an extraordinary opportunity.

“Molecular pathology takes medicine to the next level and the next stage in the revolution in cancer diagnosis,” explains Dr Gill. “At the moment, looking at cells under the microscope is still the mainstay of diagnosing and classifying cancer and this basic approach hasn’t changed in over 100 years. Looking at cancer cells at a molecular level is like looking millions of times closer than you can with a microscope.”

Dr Gill says it will soon cost about the same as a routine scan to identify a person’s unique cancer genetic sequence.

“By understanding what mechanisms are going wrong at a molecular level in the cancer, we can design drugs that target the specific mechanism the tumour is dependent on for growth,” he says. “This won’t replace conventional pathology, but it will take classifying cancer to a whole new and much more precise level.”

Australian researchers are also involved in sequencing other cancers. For more information go to www.icgc.org.

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PSA stands for prostate specific antigen which is a protein produced by the prostate gland. Its job is to liquefy semen, and small amounts of PSA are also released into the bloodstream. This enables pathologists to measure its level with a PSA blood test which can pick up increased prostate activity, and alert them to any sign of trouble brewing such as cancer.

“Blood levels of PSA are currently the best readily available biomarker for detecting prostate cancer,” say Associate Professor Paul McKenzie, president of the Royal College of Pathologists of Australasia (RCPA). “Men need to be fully informed about this test, and if they decide to go ahead then it must be interpreted properly and the results followed up.”

A/Professor McKenzie says men who want to assess their risk of prostate cancer should be offered a PSA test and a digital rectal examination (DRE) from the age of 40 years as a baseline measure of risk. The risk of prostate cancer is related to family history, age, PSA levels and DRE abnormalities. It is also the most common non-skin related malignancy diagnosed in Australia and New Zealand, and the second most common cause of cancer death in men. Predictive risk is therefore important, and can also be reassuring.

“The 50 percent of men who have PSA levels below the average have minimal risk of cancer,” explains Dr Ken Sikaris, chemical pathologist with Melbourne Pathology. “If a patient has minimal risk of cancer, they probably don’t need to be tested for another five years.”

Dr Sikaris says times have changed over the past 15 years in the way prostate cancer is managed. Fifteen years ago, if the PSA was above a certain level then a biopsy was performed. Nowadays, the PSA test may be repeated, other related blood tests performed, and the rate the PSA is rising (or falling) can be calculated to get an indication of what is happening.

“You have to make the best use of the tools you currently have,” he says. “The PSA is currently the best test for prostate cancer, but men with a decreased risk don’t need frequent testing. It’s the proper interpretation of tests and appropriate management of a discovered cancer that is important.”

Click [here](#) to read the RCPA’s position statement on PSA testing.

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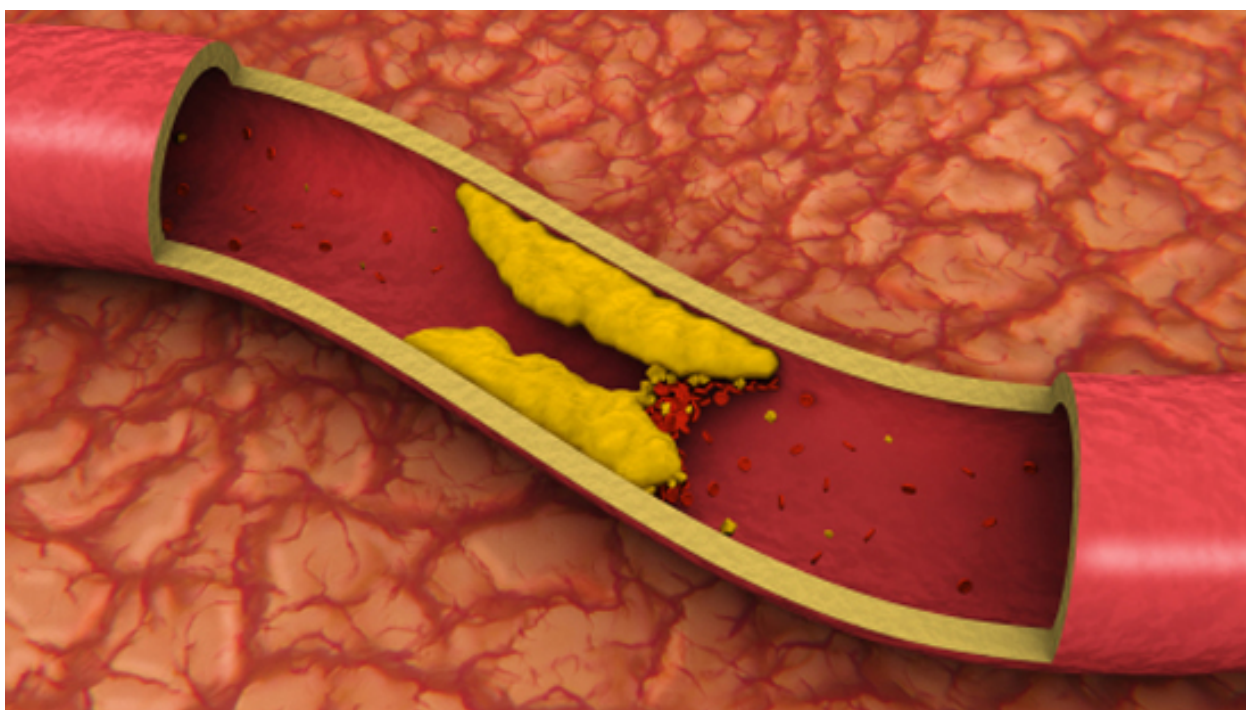
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"Normal cholesterol levels are often an excuse to continue with unhealthy eating patterns," says Associate Professor David Sullivan, chemical pathologist and Physician at the Royal Prince Alfred Hospital. "In fact, measuring total cholesterol is not a good reflection of what's going on because cholesterol is made up of good and bad components, and it's these elements and their levels that are important."

Cholesterol is a white, insoluble waxy substance the body needs to build and maintain cells and produce several essential hormones. Because cholesterol doesn't dissolve in the blood it is transported around by couriers called lipoproteins.

There are a few types of lipoproteins, but the two that are considered the most important are low-density lipoprotein (LDL) and high-density lipoprotein (HDL). LDL does most of the delivery work and is also known as 'bad' cholesterol because it sticks to the lining of the blood vessels if there's more than

the body needs. HDL is the 'good' cholesterol because it 'scours' the walls of the blood vessels to remove excess LDL. And it's the ratio of these two lipoproteins, as well as triglycerides (which is the insoluble fat transported with cholesterol in the lipoproteins), which hold the key to keeping arteries healthy.

"There really is no normal cholesterol level," says Associate Professor Sullivan. "Different people have different requirements and risk factors, and a person's blood picture changes as obesity increases. So, it's not so much a case of having a problem with bad cholesterol, but more a lack of good cholesterol and an increase in triglycerides in the blood."

This means that to get an accurate picture of what's really happening inside Dave's and Steve's arteries, pathologists need to measure the total cholesterol level as well as the level of triglycerides and good 'HDL' cholesterol in the blood. It's difficult to measure the bad 'LDL' cholesterol, so pathologists usually calculate this level based on the other factors.

"A key part of keeping cholesterol levels under control is to try to avoid unhealthy fats since they are the main culprits in artery disease," says Associate Professor Sullivan. "A good rule of thumb when looking at fat is that if it's solid at room temperature then it's probably an unhealthy fat, but if it's a liquid then it's a healthier choice. A lot of bad fat is also hidden in processed foods and in large 'liquid' amounts in hot fried foods such as chips and donuts."

So Dave and Steve may share the same total cholesterol level, but when you break it down into triglycerides, LDL and HDL, the safe bet is that Dave's cholesterol level is a healthier mix than Steve's.

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