ePathWay
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Issue #011

FEBRUARY 2012 | Published by RCPA

In This Issue

Interesting Facts

380

The estimated number of genes found to be associated with a genetic condition in a person

20,000

The estimated number of genes in a human

Welcome to the February edition of ePathWay

This month's articles have a genetic focus as pathologists and scientists from around the world prepare to meet in Sydney from 11-14 March for the Human Genome Organisation (HUGO) Meeting 2012. The RCPA is co-hosting the first day of this important gathering which follows on from its own Pathology Update conference titled 'Science in the City' from 9-11 March (more on this next month).

Genetics is revolutionising medicine in terms of diagnosing diseases and identifying treatments with one article exploring how genetics is changing the way we treat individual 'bugs'. But there are issues to address such as Medicare funding arrangements for genetic tests and the absence of expert medical interpretation for Direct-to-Consumer genetic testing.

This edition also includes an inspiring non-genetic story about a pathologist who retrieved precious histology specimens from his damaged laboratory in the aftermath of the February 2011 Christchurch earthquake.

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.

1. *Information on the RCPA Pathology Update conference can be found at http://www.rcpa.edu.au/pathologyupdate*
2. *Information on the HUGO meeting can be found at http://www.hgm2012.org*

Direct-to-Consumer genetic test results can be lost in translation

10,000

The estimated number of genes in a roundworm

Source: Centre for Genetics Education Fact Sheet 24

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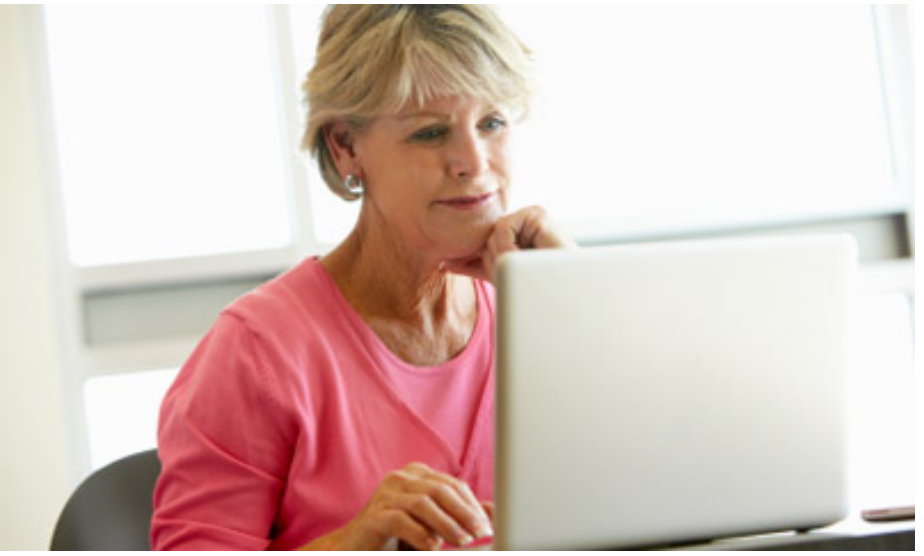

Cutting out the middleman is a growing trend. Consumers are embracing the freedom to buy almost any product or service directly from suppliers based in any country via avenues such as the Internet – including Direct-to-Consumer (DTC) genetic tests. But genetic testing is one area where the 'middleman', who should be an expert medical practitioner, really does count.

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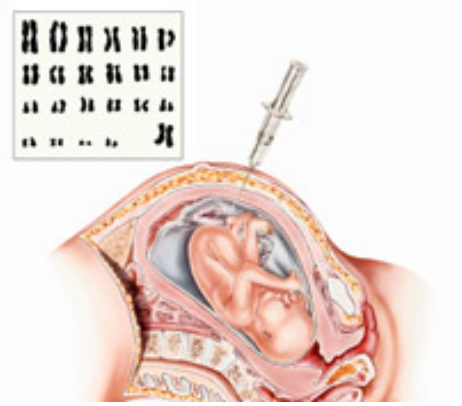
Diagnostic genetic tests offer benefits and risks for prenatal Down syndrome screening



Life throws many difficult decisions in our paths, and they don't come much harder than deciding to have an antenatal screening test for Down syndrome. These tests won't pick up every affected pregnancy, but they do sort women into high or low risk groups. Women with 'increased risk' reports are offered a diagnostic genetic test which provides the most accurate information about Down syndrome, but are the most physically invasive of the tests and carry their own set of risks.

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Direct-to-Consumer genetic test results can be lost in translation

Cutting out the middleman is a growing trend. Consumers are embracing the freedom to buy almost any product or service directly from suppliers based in any country via avenues such as the Internet – including Direct-to-Consumer (DTC) genetic tests. But genetic testing is one area where the 'middleman', who should be an expert medical practitioner, really does count.

"People may choose DTC genetic tests because of concerns about privacy, or because the information they are looking for is potentially embarrassing or may have implications for their eligibility for life insurance," explains Professor John Christodoulou, Director of the Western Sydney Genetics Program based at the Children's Hospital at Westmead in Sydney. "But it is essential that suitably qualified clinicians and counsellors help them through the process and it is not left to the consumer to try to interpret often very complex and potentially confusing results in the best way they can."

Professor Christodoulou says some DTC genetic tests can provide quite bogus results.

"They report on such things as the type of ear wax you might have, or one's ability to roll one's tongue, or the ability to detect asparagus-like odour in one's pee after eating asparagus, " he says. "Other tests claim to identify genetic markers which can then be used to identify the best nutrients to take or beauty products to use."

Regardless of what the test is for, the concerning issue is that genetic information is provided to consumers without being interpreted by a qualified medical practitioner.

"DTC companies say they are empowering people to take control of their health and their future," says Dr Graeme Suthers, Chair of the

Genetics Advisory Committee at the Royal College of Pathologists of Australasia (RCPA). “But it’s really a commercial transaction, not healthcare, and while the information may look harmless they are sending the wrong message about the use of genetic information.”

Dr Suthers says it can be difficult for the professionals to make informed decisions about genetic test results, and he is concerned that people may make uninformed decisions that interfere with their health care.

"The results from DTC genetic tests do not necessarily have the accuracy and validity that we accept as the norm for medical testing in Australia and New Zealand," explains Dr Suthers. "And even if the test is accurate, it may not be useful. For example, if a test indicates that a 50-year-old women's relative risk of breast cancer is reduced by 10 percent, this means that her risk of breast cancer in the next year changes from one in 300 to one in 330. This is a very small change in overall risk and she should not forgo the breast cancer surveillance recommended for women generally. In this context, the test has provided no useful information."

Professor Christodoulou says if a genetic test is requested by a qualified medical practitioner to answer a specific medical question, then the most appropriate test will be requested and the result will be interpreted for the consumer in a meaningful way.

“If there is no specific medical question, as often happens with DTC testing, then the tests are requested using a shotgun approach with a smattering of results. It’s then left to the consumer to identify the relevant results when they can’t even be sure of the quality and reliability of the data,” he says. “Studies have shown that the same genetic sample sent to different DTC laboratories get different results”

This raises the important issue of the lack of accreditation for DTC laboratories.

“There is no requirement for DTC laboratories within Australia or overseas to have any form of accreditation to deliver a genetic test,” explains Dr Suthers. “Anyone can perform a genetic test and send a result, and when there is no accreditation framework then the quality of the sample, transport, analysis and interpretation is questionable. I would not be willing to make medical decisions based on DTC test results because you would not know if the result is correct.”

The Centre for Genetics Education (www.genetics.edu.au) is a reliable consumer resource for genetics information.

DTC Genetic Tests is covered in ePathWay issue #001

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It's one year ago this month that Christchurch shook to a standstill after a devastating earthquake destroyed buildings and claimed precious lives. One story to emerge from that fateful day is the efforts of pathologist Dr David Roche, from Southern Community Laboratories, to retrieve unprocessed biopsies from his damaged laboratory.

"My wife, who is a Construction Engineer, said it was OK to go in, so I put on a bicycle helmet and retrieved the unprocessed biopsies. I took them home and sorted them in my garage and then sent them to another laboratory in Dunedin for processing," says Dr Roche. "Many of those specimens were irreplaceable one-off biopsies, and it would have been terrible to have lost them without being reported on."

Dr Roche says their old laboratory is now being demolished and a new facility is being built this year. Until then, histology specimens have been processed in a temporary laboratory set up in an old heating factory, some processing is done in a Dunedin laboratory and some are processed at the Gribbles Veterinary Laboratory.

"It was difficult finding temporary laboratory space because so many buildings were destroyed. We have also had a large number of aftershocks over the past year and the staff have been a bit on edge," he says. "But the new lab will mean we can rework how we do things, and we will be able to work closely with Canterbury Health Laboratories and Christchurch Public hospital, so that is a positive outcome."

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Life throws many difficult decisions in our paths, and they don't come much harder than deciding to have an antenatal screening test for Down syndrome. These tests won't pick up every affected pregnancy, but they do sort women into high or low risk groups. Women with 'increased risk' reports are offered a diagnostic genetic test which provides the most accurate information about Down syndrome, but are the most physically invasive of the tests and carry their own set of risks.

"It is important to consider the concept of antenatal screening and to think about it carefully," says Dr Narelle Hadlow, Chemical Pathologist at Western Diagnostic Pathology in Perth. "While women may opt for screening for a variety of reasons, including reassurance, antenatal screening can be a roller coaster and may be difficult to opt out of once the process starts."

Dr Hadlow warns there is also the risk of finding abnormalities other than Down syndrome with a genetic test, and is one reason why information and counselling is offered to women before the test.

Down syndrome was first described by physician John Langdon Down in 1866. Also known as Trisomy 21, it occurs when a person has three copies of chromosome 21 instead of two. Other trisomy syndromes include Edwards (Trisomy 18) and Patau (Trisomy 13), although Down syndrome is the most common chromosomal abnormality. It affects about one in every 650 babies who are born alive.

Screening tests for Down syndrome have evolved over time according to advances in medicine and the changing demographics of childbirth. In the 1970s age[1] was the only risk factor available to 'screen' women before offering them a diagnostic genetic test. The assessment process is different today.

"The risk assessment process is more complex now and may combine factors such as the mother's weight, any previous Down's pregnancy and

her ethnicity," explains Dr Hadlow. "The most common screen offered today is the combined screening test in the first trimester. This involves a blood test at around 10 weeks to measure specific maternal hormone levels, and an ultrasound at 12 weeks to measure the size of the nape of the baby's neck. This screening approach has a detection rate of 85 to 90 percent."

If the risk profile from these screening tests is considered high, then mothers are offered either an amniocentesis, where a sample of the fluid surrounding the baby is taken and examined, or chorionic villus sampling (CVS), where a sample of the tissue that will ultimately become the placenta, called chorionic villi, is taken and examined. These diagnostic tests occur around 12-15 weeks into the pregnancy.

"Between three and five percent of people who have the combined screening test, and receive an 'increased risk' report, are offered a diagnostic genetic test for Down syndrome," says Dr Hadlow. "These tests have close to a 100 percent detection rate for confirming the presence of the extra chromosome, although they do have risks associated with them."

The risks for amniocentesis or CVS sampling include membrane rupture, infection or miscarriage. Dr Hadlow says while these risk are low, at less than one percent, they are still important considerations. That's why noninvasive prenatal diagnosis (NIPD) is the goal pathologists and scientists are working towards.

NIPD techniques currently being trialed include recovering fragments of a baby's genetic information from the mother's blood circulation through a normal blood test sample. Genetic advances will probably deliver this outcome in the not-too-distant future, but for now it's a case of weighing up the risks and making an informed decision about diagnostic genetic testing for Down syndrome.

Dr Hadlow will present a talk on Down syndrome screening at the RCPA's Pathology Update Conference in March.

[1] The chance of a woman giving birth to a live-born baby with Down syndrome at 25 years is 1 in 1383. This increases to 1 in 338 for women at 35 years, and 1 in 32 for women at 45 years.

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"When we talk about bugs we mean bacterium, viruses and fungi," explains Associate Professor Vitali Sintchenko, Clinical Microbiologist at the University of Sydney Medical School and the Centre for Infectious Diseases and Microbiology at Westmead Hospital. "The first genome fully sequenced of a free-living organism was actually the Haemophilus bacteria in 1995."

Genome sequencing is a laboratory process that provides a detailed description of the sequence of the chemical building blocks of an organism in a given stretch of its Deoxyribonucleic acid (DNA). The DNA segments which carry this genetic information are called genes. All of the genes put together form a genome which carries all of the genetic information, or genotype, of an organism. Once a genome is sequenced, small changes in that sequence that may cause disease, called mutations, can be identified.

"The cost and speed of genome sequencing has dramatically improved. Thousands of genomes have been sequenced and the information entered into public databases," explains A/Professor Sintchenko. "This collaborative effort enables pathologists to determine which genes are present in certain bugs, and detect the genes that jump from one bug to another."

A/Professor Sintchenko says many bugs are very promiscuous and evolve by sharing genetic material and developing new properties. These 'jumping genes', and their mutations, can now be sequenced allowing pathologists to focus on particular subtypes.

"Before we could fully sequence genomes we only recognised one type of Hepatitis C virus," he explains. "Now we can sub-classify them into

'more virulent' or 'more drug resistant' variants, and we have learned about the association between genotype, patient outcome and transmissibility of pathogens."

Sequencing also provides information about the mechanisms of drug resistance. This enables pathologists to select the most appropriate antimicrobial agents for diseases such as Human Immunodeficiency Virus (HIV) and Hepatitis C virus.

"We now know the treatment of patients infected with genotype 1 Hepatitis C requires high dose, long-term antimicrobial therapy, while genotype 3 requires a lower dose for a shorter duration and has a higher chance of success," explains A/Professor Sintchenko. "The response to the drugs, and the chance of eradicating the viral infection, can also be predicted."

Another example of sub-classification is the genetic evidence that the Beijing strain of mycobacterium, which causes human Tuberculosis (TB), can be more transmissible, especially among young people, and linked to higher rates of drug resistance than other mycobacterium TB strains. The Beijing strain is responsible for about one quarter of TB cases in Australia.

"TB was viewed as a single entity before this genetic breakthrough. With new 'genomic glasses' we can zoom in on different genotypes such as Haarlem, Central Asia or Eastern African Indian strains of TB," explains A/Professor Sintchenko.

Genetics also plays a role in public health. An outbreak of haemolytic uremic syndrome due to Escherichia coli reported in Germany last year was originally attributed to Spanish cucumbers. Scientists in Germany and China sequenced the offending bacteria in several days. Their findings not only helped to clear the cucumbers, but also guided investigations that identified locally grown sprouted seeds and fenugreek imported from Egypt as the possible culprits!

The rise of genetics has certainly tipped the scales in favour of the medical profession's war on bugs. Understanding genetics, and keeping abreast of the rapid advancements in this area, is becoming a new challenge.

"The genetic revolution has encouraged international collaboration of clinical research to look at the relationships between microorganisms and different outcomes in order to develop more targeted therapies," says A/Professor Sintchenko. "However, more training is needed for all doctors to keep up with these new developments."

Once everyone is up to speed, it will probably be a case of the bugs can still mutate, but they can no longer hide!

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Foetal autopsies provide valuable medical information

Foetal autopsy is not a comfortable topic to discuss, but a discussion needs to happen about issues such as equity of funding and lost medical information if additional tests do not occur. One barrier is the absence of Medicare funding for these procedures because a foetus does not conform to the Medicare definition of a 'person'.

"Funding additional tests arising from foetal autopsies is one of the many issues that needs to be addressed in the area of genetics," says Mr Michael Ralston, Member of the Genetics Advisory Committee at the Royal College of Pathologists of Australasia (RCPA). "A good start would be to review the Medicare definition of a person."

Medicare only provides funding for people that are living and doesn't recognise a foetus or stillborn child as a 'person.' Professor Yee Khong, Anatomical Pathologist with South Australia Pathology at the Women's and Children's Hospital, Adelaide, and President of the RCPA, says this means additional testing following some autopsies that should happen doesn't.

"These additional tests are very expensive so they may not happen without funding assistance. If they are done in the public hospital system then they are State-funded, but otherwise there is no financial assistance," says Professor Khong. "In some cases samples from the foetus are being sent overseas because some of these tests are cheaper to perform there than in Australia."

Foetal autopsies uncover valuable information because diseases of foetuses are often different to those encountered by adults. An autopsy can confirm the cause of death and detect congenital abnormalities, genetic syndromes and the possible risk of these syndromes for other family members.

"If a foetus has a congenital disorder of glycosylation (CDG)[1] then there may be implications for future siblings because it is a recessive gene disorder. This means that future siblings have a one in four chance of being affected so it is important to know this information," explains Professor Khong. "Another example is being able to differentiate if a foetus died from either Skeletal Dysplasia or extreme growth restriction. This information would not be known if extra testing did not occur because we wouldn't be able to grow the fibroblasts for the molecular testing

of the foetus' DNA."

Mr Ralston says there is an accruing benefit from foetal autopsies which extends past the foetus' immediate family. This includes the future diagnosis and management (including prevention) of otherwise fatal or severely debilitating genetic disease in the children of at-risk carriers identified in an extended family pedigree.

"The disease ornithine transcarbamoylase (OTC)[2] can be fatal, but if a genetic test is done on the foetus or infant that has died in the newborn period, and this diagnosis is confirmed, then relatives of the foetus or infant can be tested," he says. "Future babies would then have a chance to be diagnosed prenatally and immediate neonatal management implemented."

Mr Ralston says a current government departmental review is investigating developing a national approach to genetic services, with increased equity of access one of the major benefits to hopefully come out of the review. Genetic items currently represent just over one percent of pathology Medicare schedule items. In the meantime, the benefits that accrue from additional tests arising from foetal autopsies will continue to be lost along with the 'child' unless a rational and equitable way of funding these tests is initiated.

[1] CDG is a group of inherited disorders that affects a process called glycosylation. This process helps build glycoproteins required for normal growth and function of all tissues and organs. It is now thought to be an under-diagnosed disease.
[2] OTC is an X-linked recessive disorder caused by a number of different mutations in the OTC gene. It affects the body's ability to get rid of ammonia which is a toxic breakdown product of the body's use of protein. Ammonia then accumulates in the blood and travels to the various organs of the body.

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