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When biology meets silicon

5:00 AM Saturday Jan 26, 2008

The GeneChip device. Photo / Greg Bowker.

"Getting to know your genome can help you understand a little better why you are the way you are and in what ways you're similar to or different from your family, friends and neighbours."

So says the slick video on the 23andme website which offers those with about US$1000 to spare a way to read their DNA.

The California company, part-funded by Google, is just one of several offering direct-to-consumer genetics services. Those who want to know their genome receive a collection kit with instructions on how to take a cheek swab or saliva sample which is then couriered to the company's laboratory for DNA extraction and analysis.

What they get back is an on-line report of their genetic ancestry and a risk assessment of their genetic susceptibility to a range of diseases and conditions including heart disease, several types of cancer, obesity and diabetes.

The technology that makes this possible comes from advances in both genetics and a type of microchip. Massive studies like the Genome and HapMap projects have provided new genetic libraries about what's in our genes. Surprisingly, when it comes to DNA, humans are remarkably similar. What makes us different are small copying errors in the vast DNA alphabet of around 3.5 billion letters. It's these single letter variations - "snips" or single nucleotide polymorphism (SNPs) - that are grabbing all the attention. Scientists have begun to correlate certain SNPs to a range of physical traits and other attributes - such as your reaction to some drugs and your susceptibility to some diseases. The essential idea behind the direct-to-consumer genetic services is find the "snip" and you find the risk. But looking for 10 million SNPs among around two metres of microscopic strands of DNA is no easy task. Which is where the gene chips or microarrays come in. Minuscule amounts of gene sequences "printed" on to silicon in an orderly grid, provide up to 1.8 million "probes" of single stranded synthetic DNA. When a fluorescently labelled sample of DNA is introduced to the array it will stick - "hybridise" - to complimentary gene sequences and show up as a glowing spot on the grid. The chip is scanned and the results analysed by computer software.

"As doctors, we aren't sure that the results from these personal genome services are actually helpful to people," says pharmacogenomics researcher Dr Patrick Gladding. "If you find your heart attack risk is two times the normal, will that convince you to do more exercise and eat better?" There are concerns too that there is no definitive research of what percentage of people with the disease-associated SNPs will actually get the disease or get sick.

Most of the conditions scanned for are complex and thought to be caused by multiple gene variants and interactions among these variants and environmental factors. Someone may test positive for a gene associated with colon cancer but may have several other genes that protect from the disease - which

may not be picked up by the personal genome services. Some may contract the disease even if they lack the gene.

Scientists and ethicists warn our understanding of genes is very much a work in progress. There is yet to be agreement about standards to measure the validity and usefulness of genetic markers especially those associated with disease. The worry is people could make life decisions based on incomplete or erroneous science. Some suggest users would be better off spending their US$1000 on on gym membership

But Gladding points out the technology is showing benefit for drug development and drug response. "How you respond to a drug doesn't tell you about the disease you might develop, it just tells you whether that drug will work or possibly not harm you."

The bigger concern is that we're rushing headlong into a world where both identity and destiny will be written in our genes. That raises a lot of unanswered questions. Who will keep and control this genetic information? Where will it be stored? Will we see a new form of discrimination against certain types of genes? Will consumers be able to keep their DNA information private from employers, potential spouses, insurers, and anyone else?

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Gene genie

By Chris Barton
5:00 AM Saturday Jan 26, 2008


Patrick Gladding is driven by the prospect of discovering something new. Photo / Richard Robinson.

In a modest Auckland laboratory, heart specialist Patrick Gladding is solving a genetic riddle that for some patients will mean the difference between life and death. The young researcher examines the genetic blueprints of patients to determine how they will respond to treatment.

He works at the frontier of what is known as personalised medicine, where treatment is based your unique genetic makeup. In some quarters the idea of tailoring treatment to your personal genes is seen as the next holy grail in health treatment.

It's a genetic revolution spreading beyond hospitals and medical laboratories. For around US$1000 anyone can get to know their genome better by sending a saliva or cheek sample to companies offering gene readings of their future.

While personalised genetics promises to tell you more about your ancestry and susceptibility to heart disease, Alzheimer's, cancer and diabetes, there are doubts about the scientific soundness of such services. Not to mention ethical and privacy worries about who controls the genetic libraries the technology creates.

Despite the concerns, many are saying the genome is out of the bottle. And thanks to the internet and a seemingly insatiable desire to know more about ourselves, our bodies and our health, gene-based profiling seems unstoppable.

All of this means Patrick Gladding's astonishing work has made him hot property for American research companies looking to recruit the very best scientists from wherever they can find them.

There are padlocks on the fridge to keep the fish out. It's no joke. In the first week Dr Patrick Gladding got his cold storage, someone at the hospital decided was good place to keep their whole fresh fish. He can laugh about it now, but at the time it wasn't funny. Not when you're about to begin freezing painstakingly gathered vials of DNA and other human blood samples.

It's a stretch of the imagination to call the corner of the tiny room on Auckland City Hospital's Cardiology floor a lab. But the fridge and the narrow bench lined with scientific equipment – platelet analyser, heating block, vortexer, centrifuge and pipettes – plus an indefatigable attitude, serve Gladding well enough. The tools of his trade – bought, begged and borrowed – plus some high tech collaboration with Swedish and Australian university laboratories, have put the 34-year-old research fellow on the verge of something big.

By detecting certain genetic markers – recurring codes in DNA – Gladding has found a way to predict whether coronary patients will have a positive or negative reaction to the anti-clotting drug,

clopidogrel, before it's administered. "I think it's going to have major implications for patient treatment, particularly for patients undergoing angioplasty and stenting," says Professor Harvey White, the hospital's director of coronary care and cardiovascular research.

The preliminary finding represents the holy grail for a researcher at the cutting edge of the complex field of pharmacogenomics or personalised medicine. Knowing what drugs will work with who on the basis of what is in their genes has huge implications for medical treatment as we know it. Instead of giving a drug and waiting for a reaction, doctors can look forward to a day when they can tailor treatments specifically to an individual's genetic makeup. It's a promise with two key benefits for patients - increased effectiveness and reduced adverse side effects.

Gladding is something of an oddity at the hospital. Although he's a trained cardiologist, he's opted not for the six figure salary he could command as a senior specialist, but for the relative poverty of immersing himself in pure science. For the past 14 months he has lived off cobbled together research grants from which he also has to pay for his equipment and the services he employs in his work. Is he mad?

"Every now and then I wake up in the morning and wonder what the heck I'm doing. My wife sometimes wonders that. And I look at my kids and that we live in a very average home ... ", says Gladding trailing off wistfully.

But then he remembers what drives him. "The prospect of discovering something new is very exciting - you can help more than one person. You might influence the way lots of people work. The excitement of a discovery becoming something useful far outweighs the money to me."

Pharmacogenomics is still in its infancy, but it does have some success stories, such as herceptin. The breast cancer drug helps one in five women who take it - women who, it turns out, have a mutation in their tumour cells that clearly differentiates them from other types of cancer. What's unusual about herceptin is that the drug is sold with a diagnostic test which determines who will benefit.

Gladding is developing a similar type of test for clopidogrel.

"He can identify those patients where clopidogrel works and those patients where it doesn't," says White. "He's even gone a step further - looking at the patients where it doesn't work and whether a bigger dose may help."

The concept of targeted drugs has obvious benefits for patients. But it has economic implications too. Herceptin is one of the most expensive drugs on the market. That's because it breaks with the blockbuster, one-size-fits-all model of drug development. Like the art house movie, personalised medicine caters to a smaller audience.

If a test such as Gladding's was applied to a large clinical outcome study and proved useful, it could impact on the $7 billion international market for clopidogrel.

On the plus side, a test determining who the drug works for would save money for hospitals and drug agencies like Pharmac. The drug companies might not be so happy. Seeing as much as 20 per cent shaved off their sales is not something they're likely to take lying down.

Whatever the hurdles ahead, late last year, when the research results for those resistant to clopidogrel

indicated a tight correlation with genetic markers, Gladding felt pretty good. "I was beaming for a couple of days. But no one believes it yet or thinks that it has value."

Gladding is about to show them. The next phase of his study involves recruiting a second group to validate the test response to clopidogrel. He's also in the process of writing up the research for publication and patenting a genetic test related to his discovery - something he's paying for himself.

Down the corridor in one of the high tech operating theatres a patient is on the table. High tech x-ray imaging machines on robotic arms swing around the huddle of gowned-up cardiologists and assistants. In startling clarity, magnified arteries amid a spidery network of blood vessels, pulse on screen under the watchful eyes of the surgical team guiding a balloon catheter on its path.

It's here, among routine angioplasty and pacemaker procedures, that Gladding's work began. Taking blood samples from coronary patients given clopidogrel to stop microclots forming in the mesh stents about to be placed in their narrowed arteries, Gladding used a portable platelet analyser to test for stickiness in the blood at intervals after the drug was given.

The results told him which patients were "responders" or "non-responders" to the drug. Other studies indicate that for 70-87 per cent of the population clopidogrel works fine, but for the remaining 13-30 per cent, it might not. Similar statistics show up with aspirin and other heart medications. For the non-responders, clotting of the stent is serious and can be fatal. When it occurs, another operation or medication is quickly required.

Gladding also extracted DNA from each of the blood samples and sent it off for mass spectrometry analysis, first to Sweden's Uppsala University and then to the Genome Research facility in Australia.

He focused on several genes which he hypothesised might be relevant to the function of the drug. That helped narrow down the DNA search. Even so, it was like looking for a needle in haystack.

Gladding was looking for "snips", researcher shorthand for SNPs (single nucleotide polymorphisms) - single letter variations in the genome alphabet. Thanks to the Human Genome Project, completed in 2003, we now know that when it comes to our 23 chromosomes, around 26,000 genes, and 1.8 metres of DNA double helix strands, we're 99.9 per cent the same. Snips (SNPs) are the 0.1 per cent bits of DNA code that make us different.

There are about 10 million common SNPs, each occurs roughly every 1200 letters or so, in the 3.5 billion letters that make up the genome - a nine-storey stack of telephone books. As Gladding points out, that makes for a lot of reading. But the task is made easier by technology that scans and identifies genetic sequences and computers that process the vast amount of data gathered.

In fact the technology is getting so good that gene chips, (microarrays) are being used to provide genome mapping services direct to consumers. For around US$985-US$2500 consumers can send in a cheek swab or saliva sample and receive their gene profile that not only tells about their ethnic ancestry, but also rates their risk for certain conditions including asthma, Alzheimer's disease, myocardial infarction (heart attack) and diabetes.

Similar to microprocessor technology, which doubles the number of transistors that can be crammed on to a silicon chip every 18 months, gene chips are also developing at ever-increasing densities. The latest has 1.8 million "probes" of synthetic DNA layered in an array of tiny gene dots on silicon wafers.

(See: "When Biology Meets Silicon").

Because Gladding was already focused on a number of genes, he didn't use microarray technology for his search, opting instead for the more traditional and less costly mass spectrometry. His study was also relatively small - just 60 patients. But it was enough to compare SNPs in the patients resistant to clopidogrel with those for whom the drug worked fine.

What he found was several novel SNPs, not previously associated with the drug response. And that the non-responders all shared SNPs that were mostly absent in the responder group. Of more significance is that something can be done for non-responders - a bedside test to identify them and then decide on the appropriate treatment.

Gladding also needs to run his study with larger numbers - something he could achieve overnight if he could convince drug companies to test the DNA they have banked from other clopidogrel studies. "The problem is drug companies don't like this technology at all, because it means some people won't be getting the drug. They want the drug to be applied to everybody," says Gladding. But there are signs that, whether the drug companies like it or not, personalised medicine is here to stay.

The United States Food and Drug Administration sees pharmacogenomics as way to improve drug safety and has developed guidelines for the collection of DNA data for new drug trials. It's clear too that the drug companies aren't about to ignore pharmacogenomics either. There are also some ironies. A piece of equipment used in Gladding's blood stickiness research - the platelet analyser - was a donation from drug company Sanofi Aventis which also holds the patent for clopidogrel.

At Auckland University's Proteomics laboratory Gladding views graphical representations of some of his blood samples that have been "smashed" into electrically charged fragments and measured as they fly through parabolic arcs inside one of the lab's mass spectrometers. Here, he's looking not for genetic markers, but for proteins produced from the heart in patients under going angioplasty. The hope is to find new proteins that could be a marker for damage to the heart. An offshoot of his clopidogrel research, it's the type of high tech collaboration he would like to be doing more of - searching for molecular clues about how the heart functions in clinical environments.

The buzzword for what Gladding does is translational research - bridging the gap between doctor and scientist, clinical medicine and science. It's a hard road at the best of times and even more difficult in New Zealand, which lacks the collaborative infrastructure for pharmacogenomic research.

He looks on with envy at Australia's IMBcom, an offshoot of the University of Queensland's Institute for Molecular Bioscience. There, doctors work half time in a hospital and half time in their science laboratories. Gladding craves the collegiality - being able to walk down corridors, bump into fellow scientists and chat about things. Not to mention IMBcom's team of intellectual property lawyers tasked with insuring a payoff for every dollar invested.

It's a world Gladding may soon get to experience. He's been offered a research fellowship at the Scripps Research Institute near San Diego, one of the United States' largest private, non-profit research organisations. There he would be among an army of professors, postdoctoral fellows, PhD students, laboratory technicians, and support personnel. Not to mention having access to state-of-the-art equipment, including a Cray supercomputer, high-performance nuclear magnetic resonance spectrometry instruments, and a DNA sequencing laboratory. The downside is living like a student again and uprooting his family from New Zealand.

Not that he's complaining about what he's been able to achieve here. Working in the hospital gives him invaluable access to real world patients. His research has been recognised in a number of Australasian investigator awards and is strongly supported by several of the hospital's high profile cardiologists. And he's indebted to the Green Lane Research and Education Trust, the A+ Trust and others for funding him.

While the hospital gives plenty of support through its Research Office, including a bio-statistician to verify his results and a research co-ordinator to guide him through bureaucratic frustrations, it isn't exactly geared to research. "People voice support for research, but it's not a major driver at the hospital," says director of coronary care White, who sees innovation and optimising patient care through work like Gladding's taking a back seat to cost-cutting.

To the administration Gladding is seen as a cost - even though he regularly teaches trainee doctors in bedside and electrocardiogram skills. "I just do that because that's part of what being a doctor is - I enjoy it and I think it's important." But he also has to pay the going rate for the hospital resources he uses. That includes $200 per DNA extraction - something he got down to $6 by buying his own equipment, taking a short course in molecular biology and doing it himself.

This No 8 wire Kiwi ingenuity attitude is admirable, but the question in Gladding's mind is where to next? Despite nearly a decade of talk about New Zealand developing its biotechnology sector as one of the pathways to a knowledge economy, he despairs at times at how little has developed.

What does he want? "To work among a network of people to allow constant and further development of these kinds of ideas."

If Gladding takes the Scripps job, it's a fair bet his skills will be in high demand off shore. The question someone has to ask is whether another brilliant researcher will be joining New Zealand's brain drain.

PERSONAL GENOME SERVICES

* 23andMe, available in North America and Europe for US$999, www.23andme.com. * deCODE Genetics, available globally for US$985, www.decodeme.com. * Navigenics, available later this year for US$2500, www.navigenics.com

By Chris Barton

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Painkillers could increase risk of stroke

By Martin Johnston
5:00 AM Tuesday Mar 11, 2008

A new Auckland study has shown that aspirin's blood-thinning ability is inhibited by some anti-inflammatory painkillers.

Many thousands of New Zealanders take aspirin to reduce their risk of having a heart attack or stroke. Those also taking non-steroidal anti-inflammatory drugs (NSAIDs) that performed poorly in the study are potentially increasing their risk.

Aspirin is one of the most commonly prescribed drugs. It reduces the platelet aggregation - the blood's stickiness - in most people.

The study of 24 people - whose first author is Dr Patrick Gladding, a research fellow at Auckland City Hospital's Green Lane Cardiovascular Service - found that naproxen, ibuprofen, indomethacin and tiaprofenic acid blocked aspirin.

It is the first study to find the effect with naproxen and tiaprofenic acid.

Celebrex and sulindac did not block aspirin, and of the six non-steroidals tested may be the drugs of choice for patients requiring aspirin and NSAIDs, says the study, published on-line in the *American Journal of Cardiology.*

Dr Gladding said United States medicine regulators had placed a warning on ibuprofen packaging in 2006 warning of the interaction.

His supervisor for the study, cardiologist Dr Mark Webster, said yesterday the study's main message was that if patients took aspirin to reduce the risk of stroke and heart attack, and an NSAID, they should take the latter just once a day and about 30 minutes to an hour after the aspirin.

"The other message is for prescribers to be aware of the interaction and accept that non-steroidals are probably not without some cardiovascular risk in general."

Dr Stewart Jessamine, the senior medical adviser of state medicines regulator Medsafe, is aware of earlier research on the interaction between aspirin and NSAID but has not yet seen the new Auckland study.

"We'll look at it to determine if it needs to go to the Medicines Adverse Reactions Committee to see whether there is any advice that needs to be issued around taking aspirin and these medicines together."

By Martin Johnston

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A cure, but not for all

By Chris Barton
4:00 AM Saturday Aug 29, 2009


Dr Patrick Gladding with a 3D laser etching of a double helix, or DNA. Photo / Paul Estcourt

Chances are, if you're admitted to hospital with chest pain from clogged arteries, you'll rapidly become familiar with a lifesaver called Clopidogrel.

The drug, which also goes by the name Plavix, is used in a range of heart diseases as well as for circulatory conditions and in the treatment of stroke.

It saves lives by stopping blood clots forming and is often used in conjunction with other heart procedures such as angioplasty and stenting.

What's less well known is that the drug has to interact with enzymes from your liver in order to work. Unfortunately, by a quirk of genetic fate, some don't have the ability to make these enzymes and so they don't respond to the drug.

For this group – which can be up to 30 per cent of those given the drug – the chances of recovery are not good. Also not well known is that Maori and Pacific people are much more likely than Europeans to have the genetic variant that causes Plavix not to work.

The answer seems obvious.

Test for the gene before you take the drug. And if you're a "non-responder" pursue an alternative drug treatment. Until recently, such an option was a future science fantasy. But, thanks to groundbreaking New Zealand research, you can have the genetic test done for about $200 and get your results in about 24 hours.

Lamentably, hardly anyone knows about it, and even though such a test could save lives, it's not something you'll be offered in New Zealand hospitals. Not yet.

But as research continues to show positive benefits from tailoring drugs to your genes, it's a situation that may be about to change.

Pharmacogenetics. It's a place where drugs, biology and technology collide. At its frontier is the prospect of the "US$1000 genome" – an individual's entire DNA sequence on a computer chip – a future that some claim is as little as two to three years away. Medicine, but not as we know it.

While it's now possible to know and hold the blueprint of one's fate, having such knowledge isn't always helpful. James Watson, when he was presented with his genome recorded on two DVDs, insisted that the information about his APoE gene, an indicator for Alzheimer's, was removed. Watson reasoned there was little point knowing about such a risk if there was nothing he could do about it.

It's an argument that leads many to question the benefit of direct-to-consumer online services such as deCODE Genetics and 23andMe which encourage people to send in a saliva sample and for around US$1000 ($1458) get a picture of some of their genetic quirks and glitches.

Sometimes knowing one's susceptibility to conditions such as cancer, heart disease, diabetes and mental illness may be useful, but when diagnostic ability outstrips therapeutic ability, all one may end up getting is increased anxiety.

There are privacy problems too - about where and how such information should be kept, plus issues around who should have access to information that could have profound effects on insurance and employment.

Dr Patrick Gladding, a cardiologist at Auckland hospital, stays away from such ethical conundrums by focusing on genetic variants that can make a difference.

The *Herald* last spoke to Gladding 18 months ago when he had just completed a research study of heart patients' response to Clopidogrel related to a number of genetic markers.

Since then Gladding's findings have been confirmed by several other studies, and it is now well accepted that how well Clopidogrel works does indeed depend on certain genes.

In June the United States Food and Drug Administration changed the way it labels Plavix, adding new pharmacogenetic information. The label now states that patients with a genetic variant of the "CYP2C19" gene have a significantly increased risk of heart attack.

But while the FDA clearly acknowledges the effect of genetic variants, it stops short of the next step - recommending that patients undergo a genetic test - before taking the drug.

The FDA did the same with dosage information for the blood thinning drug Warfarin which it acknowledged in 2007 was dependant on genetic variants.

It has since approved a genetic test which identifies individuals who metabolise Warfarin more slowly than normal, but hasn't put a requirement on the Warfarin label that the test be carried out.

Gladding faces similar frustrations in New Zealand. Working with Linnaeus, a laboratory in Gisborne, he's ready to offer genetic marker tests not just for Clopidogrel, but also for Warfarin and cholesterol-lowering statin drugs used in the treatment of heart disease.

Tests which not only improve the efficacy of the drugs - in the case of statins by predicting adverse effects such as muscle wasting - but which also save lives.

While he's in discussions with New Zealand's drug regulator Pharmac, he's yet to get any official support.

"Anything that targets any pharmaceutical to the right people has got to be looked at very seriously," says Pharmac medical director Peter Moodie. "In principle we continue to be very interested in that technology."

Last year Pharmac funded 27,000 prescriptions of Clopidogrel at a cost of $2.8 million. Moodie says the

next step in assessing the new information about Clopidogrel or any other personalised medicine is complex - an analysis of the cost of the genetic test, the benefits both in terms of efficacy and lives saved, and the cost of alternative drugs for non-responders.

In Clopidogrel's case, the likely replacement candidate is Prasugrel, which is yet to have a funding application in New Zealand.

It's also likely to be more expensive - about $150 per month compared to $30 per month for the now "off patent" (generic Clopidogrel) Plavix.

The cost benefit equation is further complicated by Pharmac decision-making criteria to assess the impact of a particular disease or therapy on Maori and Pacific people.

Gladding and others have already done preliminary research which shows the genetic variant affecting Clopidogrel is more prevalent in Maori and Pacific populations. Similar studies have also shown the variant to be more common among African Americans and East Asian populations.

Gladding had also done research which indicates it may be possible to overcome the non-responder effect to Clopidogrel by an increased dose.

"The increased dose showed an effect on the sticky platelets in the blood. But we don't know yet whether upping that dose is a good thing. It could make you bleed more or it could save you from a heart attack. More research needs to be done."

The unfinished research is frustrating for Gladding who is about take up a position either in Australia or the United States to complete his specialist training in cardiology. "Essentially I ran out of funding money to keep the impetus alive."

He's hopeful others will pick up where he left off. In the meantime, Gladding has formed a company, Theranostics, to provide pharmacogenetic tests in New Zealand. Ultimately he'd like to start a DNA "biobank" here to further the research, which he believes could play a significant role in improving heart disease outcomes for Maori and Pacific people.

At present the only routine personalised medicine test done in New Zealand is for azathioprine - used in autoimmune conditions such as rheumatoid arthritis and inflammatory bowel disease.

"That's because one in 300 patients are unable to metabolise the drug and can basically be poisoned if you give them the standard dose," says associate professor Martin Kennedy director of the Carney Centre for Pharmacogenomics in Christchurch.

Kennedy and clinical pharmacologist Professor Evan Begg, also with the centre, agree the latest research on Clopidogrel looks compelling for genetic testing.

But they both stress the importance of detailed analysis of such genetic associations with drugs before proceeding. Drug interactions and a host of other factors can also play a big part.

"There's been a lot of hype and not much return from a clinical point of view," says Kennedy. The centre's research on antidepressants, for example, while useful in explaining the mechanism of the drugs, is yet to uncover genetic variants that make a significant difference to drug response.

The research on azathioprine, on the other hand, has looked at the way the drug is metabolised and found several genetic differences that do impact on patient responses.

The challenge of pharmacogenetic research, says Kennedy, is to prove they can make a difference to patient care.

By Chris Barton