

## Made-to-measure medicine

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The one-size-fits-all approach doesn't work in fashion and it doesn't work in health care either. A treatment that's helpful for one person could be useless – or even deadly - for another. But the days when medicines were designed as though we all respond the same way are rapidly coming to an end.

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Your doctor has just handed you a prescription. You've forked out your hard-earned cash to get it filled at the chemist, taken the remedy as directed, and you eagerly await its beneficial effects.

Don't hold your breath. Most medicines on the market work in fewer than half the people who take them.

'I wouldn't say that most drugs don't work,' an executive from pharmaceutical giant GlaxoSmith told Britain's *The Independent* newspaper in 2003. 'I would say that most drugs work in 30 to 50 per cent of people.'

Not only does this mean up to seven out of every 10 people are not getting the health benefits they expect from their medicines. It's also a massive waste of public money. In the last few years, taxpayer funding of pharmaceuticals has expanded faster than almost any other area of healthcare in Australia. Yet the bulk of these resources are being spent on drugs that don't work effectively. So what's the solution?

The answer could lie in a burgeoning area of research aimed at personalising medicine. Rather than assuming there's a standard response to a drug, individuals would be expected to react differently, depending on their chemical makeup. Once that's been established – by genetic tests on a blood sample – doctors could readily determine what medications will or won't work for you, or how much of a medication you really need.

'It's about going from a blunderbuss approach to a more targeted approach,' says expert Dr Stephen Boyages, principle researcher at the Diversity Health Institute at Sydney's Westmead Hospital.

Research in this field – known as pharmacogenetics – is currently being conducted in many different areas of medicine, and screening tests and drugs are already beginning to trickle onto the market (see box).

One of the very first examples of pharmacogenetics in action came about in the late 1990s with the breast cancer drug Herceptin. It slows the growth of cancer by blocking an oestrogen receptor on breast cancer cells. This type of receptor, called HER2, is associated with particularly aggressive forms of breast cancer. What's more, breast cancers cells with the most copies of the HER2 gene spread the fastest. About 25 per cent of women with breast cancer have too many copies of this gene, and only these women can be treated with Herceptin.

'When Herceptin is applied to the general population of women with breast cancer, the response rate is only about six per cent and therefore it would never have really gotten up in clinical trials,' says Westmead Hospital's Dr Stephen Boyages. 'But when you apply it to women who are positive for HER2, the response rate is close to 100 per cent.'



## Liver load

The unique combination of genes you inherit from your parents contains recipes for proteins that influence every aspect of your bodily workings. In the case of your response to medicines, one of the most profound ways in which genes exert their influence is through proteins called enzymes in the liver, whose job it is to metabolise – or break down – drugs.

Depending on what version of a particular gene you have, your enzymes could be metabolising drugs very efficiently – and therefore quickly – or less efficiently, and therefore more slowly. This in turn influences how long an active drug is circulating in the body, and therefore the dose needed to elicit a given effect.

Says Dr John Miners, Head of Clinical Pharmacology at Flinders University: 'We can have some individuals in the population who are super metabolisers, and they therefore need very high doses of a drug. And there are those individuals who essentially lack metabolic activity and conversely they need very low doses of a drug.'

The variability throughout the population is huge – as high as 500 fold – which translates to dramatic differences in the appropriate dose.

'There's a drug we use in the treatment of angina [suffocating chest pain] called perhexiline,' Miners says. 'For what we call normal metabolisers, the population average dose is two and a half tablets per day. People who are poor metabolisers only need a half a tablet of perhexiline *per week* to get the same effect.'

The implications of this massive variation between individuals are enormous – not just in terms of maximising a drug's desired effects, but also minimising its undesirable effects. Adverse reactions to drugs are one of the leading causes of hospital admissions in Australia.

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## Toxic overdose

In some instances an unintended 'overdose' might even be fatal. An example is the drug Clozapine, used to treat psychosis – a disorder which can involve seeing or hearing things that aren't real as well as having delusions or false beliefs.

Clozapine is highly valued by doctors, but its side effects can be severe.

'It's a unique drug, and it does tend to make people recover when other drugs just do nothing,' says Dr Tim Lambert, an Associate Professor in Psychiatry from the University of Melbourne.

But one per cent of people cannot metabolise the drug properly and so receive what is effectively an overdose. The result is destruction of their immune systems. This leaves them prone to infections which can be life threatening. And there's no way of knowing who is at risk.

'If it wasn't for the fact that clozapine is so unique, we would have drop-kicked this medicine 700 miles as being too dangerous,' Lambert says.

With Michael Murray, a Professor of Pharmacy from the University of Sydney, Lambert is trying to develop a genetic test to determine which patients have the 'toxic' gene profile and so should avoid the drug. The toxic profile is based on variations in a family of liver enzyme genes known as CYP.

'If there was investment in working out your personal metabolic profile, then for the rest of your life you could say "this is my profile" and your doctors could tell you that you need to be cautious with the following medicines,' Lambert says. 'So that's the future.'



## Improving cancer treatment

One area of health care in which ‘made-to-measure medicine’ should be especially beneficial is cancer treatment says Dr Ross McKinnon, Associate Professor of Pharmacy at the University of South Australia, and leader of the South Australia Clinical Pharmacogenomics Initiative.

‘Cancer drives a lot of innovation because current therapy is limited in a number of ways. It’s toxic, it doesn’t work in everybody, it’s expensive, and it’s a disease that affects one in three, one in four people.’

He’s currently working with a drug used in late stage breast and bowel cancer, called Xeloda. One in five people taking this drug develop a side effect called hand/foot syndrome, a reddening and swelling of the palms and soles of the feet which can be tender and limit mobility. Again, this toxicity develops in some people because of genetic variations in liver enzymes that metabolise this drug.

‘The current practice is you simply dose the drug based on body weight, which we know is not a good indicator,’ McKinnon says. ‘If a patient goes toxic, you simply reduce the dose. But of course, by that point the toxicity has already happened, and the patient has lost mobility. We don’t consider that to be optimal use of that medicine.’

His group is hoping to find a better way of calculating the correct dose for a patient and so avoid the toxicity.

‘There are a number of genes involved and its relatively complex, and at the moment we’re trying to piece it all together.’



## Fighting addiction

The benefits of this kind of research could even help fight drug addiction. Methadone substitution programs, used to treat heroin addicts, can be highly effective. Methadone acts on the same receptors in the brain as heroin, allowing the user to come off the drug without experiencing side effects. But about a third of patients opt out of these programs. Professor Andrew Somogyi, from the Department of Clinical and Experimental Pharmacology at the University of Adelaide is looking at possible reasons.

Preliminary studies suggest individual differences in the cell machinery involved in processing drugs might be to blame. These include receptor and transporter molecules that ferry drugs in and out of cells. Just like a lock and key, a drug may fit one person’s receptor and transporter molecules better than another person’s, and therefore the drug is more effective for that person.

People who drop out of methadone programs are more likely to have a mutation in a gene called OPRM1 that codes for an opioid receptor. It’s thought this faulty receptor makes them less receptive to methadone, and therefore less likely to stay in the program.

If this proves correct, the ultimate aim would be to establish the genetic profile of an addict before they are put on methadone.

‘You could then say “Well if you’ve got the mutation, methadone is probably not the best substitute opioid for you,”’ Somogyi says. Another opioid substitute called buprenorphine – which acts at a different receptor – could likely be used instead.



### Cost or investment?

So how soon can we expect to reap the rewards of this new technology?

'If you roll the clock forward in 10 years time I think pharmacogenetics will be commonplace. And in about 20 years time I think it will be standard,' says Westmead Hospital's Stephen Boyages.

Supporters of the technology point out that the cost of genetically profiling a patient will likely be more than offset by the savings in assessing and treating drug side effects and switching medications. Nonetheless, there is still a considerable research investment needed before 'personalised prescribing' can become widespread.

Scientists have already worked out the order of building blocks in the entire sequence of human DNA. But they still need to identify which segments – genes – are associated with particular drug responses. Changes in just one building block of a particular gene could be critical to how an individual fares when given a particular drug. Establishing the link between each of these and the effect on a person remains a mammoth task.

'The question is, as a society, do we see this as a cost or an investment?' Boyages says. 'That's an interesting debate that we're going to have to have.'

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