PHARMACOGENETICS

The right drug for you

Personalized prescribing is gaining momentum, but is there enough evidence for it to become standard clinical practice?

BY LIAM DREW

For ten-year-old leukaemia patient Jason Saunders, the usual chemotherapy was not going to work. Given the standard drug treatment, there was a strong chance that toxic metabolites would build up in his body and make him sick, requiring a break in his therapy that would allow the cancer to return.

This is because Jason is one of the 10% of Caucasians with a genetic variation that reduces his ability to metabolize thiopurines, the drugs most commonly used to treat acute lymphoblastic leukaemia. Rather than having two high-activity copies of the *TPMT* gene that produces the enzyme responsible for

metabolizing these drugs, Jason has only one.

Luckily for him, the doctors at St Jude Children's Research Hospital in Memphis, Tennessee, knew that. When he was diagnosed with cancer, one of the first things his physicians did was take a sample of his blood to assess how he might respond to the drugs. As a result, Jason was given a lower dose of thiopurines than normal, and he tolerated the therapy without needing a break. He is now in remission.

Testing leukaemia patients for their *TPMT* status is one of the most common examples of treatment being tailored to match patients' genetics, so robustly does it predict the likelihood of adverse effects from thiopurines. The test is now mandatory when starting this type

of chemotherapy in many places, and it is also recommended before using thiopurines to treat other conditions, such as inflammatory bowel disease and rheumatoid arthritis.

Tests are normally performed only when a drug needs to be prescribed, but Jason's experience was different. Instead of testing only his *TPMT* status, he was screened for variability across a host of genes involved in various drug responses, as part of the hospital's PGEN4Kids scheme. The results were then incorporated into his health records. If he is ever prescribed another drug for which those genes can predict an adverse response, the information will be presented to his doctor immediately. The choice of which drug to use, and at what dose,

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can be made immediately, with no further testing or waiting required.

To get to this point, St Jude and a few other research hospitals that are piloting similar schemes have had to develop a great deal of infrastructure, train their clinical staff in how to respond to genetic data, and secure the significant funding these schemes require. It was once a distant hope, but now there is optimism among St Jude's doctors, pharmacists and geneticists that they have a clinical programme that allows genetic information to be routinely used to personalize drug selection and dosing.

As St Jude oncologist Jeffrey Rubnitz talks about Jason's treatment, there is no thrill of the new. The way his treatment was modified according to genetic risk factors is just the way they do things. But in the outside world, clinicians and health-care providers alike are watching closely to decide if this approach to pharmacogenetics is really ready to become standard clinical practice.

LONG TIME COMING

The idea behind pharmacogenetics — that a person's genes influence their responses to medicinal drugs — is not new. Its origins are

usually traced to geneticist Arno Motulsky of the University of Washington, Seattle, who in 1957 published an article discussing the implications of evidence that adverse reactions to the antimalarial drug primaquine and the muscle relaxant suxamethonium chloride are heritable and linked to deficits in the activity of specific enzymes.

Over the decades, the number of gene variants that have been found to influence drug responses has steadily increased. Most of the genes encode enzymes that, like TPMT, metabolize one or more drugs. Some variants were found to make drugs toxic; others rendered certain drugs ineffective. As the list grew, so did expectations. By the 1990s, it was hoped that genetic screening could soon establish an era of personalized prescribing that would dramatically improve treatment outcomes.

In practice, however, only a handful of specific tests are routinely used in the clinic today. Perhaps the most celebrated involves the antiretroviral agent abacavir, which is prescribed to people who have HIV. Up to 10% of Caucasians carry a particular version of an immune-system gene called *HLA-B* that gives them a 50% chance of experiencing a life-threatening hypersensitivity reaction to abacavir. As is the case with several gene variants that affect drug responses, the problematic variant of *HLA-B* occurs at different rates in different ethnic groups. Fewer than 3% of people in African and East Asian populations carry the variant, but in India it can be as high as 20%. Within a few years of the risk allele being identified in 2002, clinics started screening for it before commencing antiretroviral therapy, offering alternative medicines to those with the problematic variant. This slashed the incidence of hypersensitivity, and *HLA-B* screening is now standard care for HIV patients.

However, a series of disappointments dampened the field's headier early ambitions. Several high-profile clinical trials failed to produce the clear evidence in support of pharmacogenetic intervention that had been anticipated. Also, the discovery rate of genes that underlie adverse reactions has slowed; the scale of genetic influence on drug responses is rather lower than was once imagined. Currently, variations in around 20 genes provide useful predictions of reactions to 80–100 drugs — about 7% of drugs approved by the US Food and Drug Administration.

Proponents of pharmacogenetics think that even this information about these relatively few drugs offers the chance to significantly improve patient care, because the drugs account for 18% of all US prescriptions. But underwhelming trial results have held back

clinical implementation. Some pharmacogenetics advocates argue that genetic tests are subjected to unreasonably high standards before being allowed into the clinic, but critics say that there simply is not enough evidence of benefits.

FOLLOW THE LEADER

Part of the purpose of St Jude's PGEN4Kids programme, says pharmacist Mary Relling, the project's leader, is to demonstrate to the wider medical community that pharmacogenetics can be implemented in the clinic. "We decided if we can't do it here, then you can't do it," Relling says. "Let's stop arguing about whether to do it and just show how to do it."

The programme, which is funded in part by the hospital and in part by the US National Institutes of Health (NIH), is offered to all incoming patients. For those who sign up — and 97% do — it examines 230 genes that encode proteins involved in drug responses. It is unclear how variants of most of these genes influence drug responses, if they do at all, and most of the data are kept for research purposes, away from the clinics. But results from 7 genes that robustly predict reactions to 23 different drugs are fed directly into the hospital's electronic health records, so any problems that patients might face are conveyed automatically to their doctors at the appropriate time.

The pre-emptive nature of the screening is important. Most doctors that use pharmacogenetic tests have to delay writing a prescription until they get the test results. But by acquiring patients' pharmacogenetic profiles when they are first admitted, "you don't have to think about testing every time you're thinking about prescribing a drug," says Relling.

Stuart Scott, a geneticist involved in a similar scheme at Mount Sinai Hospital in New York, agrees. He is frustrated that pharmacogenetic testing is often not used until after a patient has had problems with medications. "At that point I don't know if it's having much benefit," he says. "Pre-emptive testing is the way to go."

As it becomes cheaper to examine DNA, a one-off screen of many genes becomes more cost effective than ordering specific tests when the need arises. But even though testing is becoming simpler and less expensive, equipping physicians to deal with the results remains a considerable challenge. Another central aspect of the St Jude programme is therefore to provide doctors with unambiguous instructions on how to proceed if an issue is flagged.

To achieve this, the hospital uses guidelines developed by the NIH-funded Clinical Pharmacogenetics Implementation Consortium (CPIC), which Relling also leads. This is an international group of pharmacogenetics experts who have so far produced detailed practical advice on 33 drug–gene pairs. They began in 2011 with those that have the strongest case for being used in patient care (*TPMT*'s relationship with thiopurines was the first),

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Mary Relling (left) is trying to show that pharmacogenetics can improve outcomes for patients.

and are working through identified genes at a rate of about three or four a year, each of which may relate to multiple drugs.

One recent publication, for example, explains how to prescribe several related antidepressants to patients with common variants of the genes *CYP2D6* and *CYP2C19*, which affect the metabolism of these drugs. It recommends avoiding certain antidepressants in some patients, or reducing the dose by 50% if they are deemed essential. Relling hopes that St Jude's health records will eventually contain information on all of the genes that CPIC views as actionable.

BURDEN OF PROOF

The screening programmes being pioneered at leading US hospitals are resolving many of the practical issues that once restricted the clinical use of pharmacogenetics. But for them to become routine elsewhere, health-care funders need to be fully convinced of their value.

"We have a lot of science that is really good. We have a lot of growing infrastructure and growing education," says Scott. "But these programmes that are doing implementation are funded by research grants." The extent to which health-care providers are willing to financially support clinical pharmacogenetics will have a significant effect on its future.

There is a feeling among those in the field that they have done enough: that the science is solid, and that numerous observational studies have shown the value of clinical implementation. Relling says that the scientific case for PG4Kids is overwhelming. "It would be unethical to withhold these tests," she says.

Munir Pirmohamed, a clinical pharmacologist at the University of Liverpool, UK, thinks that pharmacogenetic tests are held to unreasonably high standards — a bias he calls "genetic exceptionalism". A patient with kidney failure will

have that taken into account during drug selection and dosing as a matter of course, explains Pirmohamed, but a genetic variation that affects drug metabolism to the same degree is held to a higher standard of proof. "People ignore it. People say you need a randomized controlled trial," he says. "That's unreasonable."

But not everyone is convinced. James Evans, a medical geneticist at the University of North Carolina at Chapel Hill, urges caution. "We have to be careful," he says. "We need evidence of benefit before we implement."

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The field of pharmacogenetics has not produced compelling evidence by using randomized control trials — the gold standard for evidence-based medicine. Evans has been outspoken about the bloated expectations that surround genomics-based medicine and is blunt about what would best deliver evidence. "We need to use pharmacogenetics and not use pharmacogenetics, and see if there's a benefit," he says. That will entail studies of the sort that showed that one particular type of pharmacogenetics, involving the anticoagulant drug warfarin, was not useful, he adds.

The warfarin case is instructive. The rates at which individuals metabolize this drug vary widely. Break it down too quickly and it will not have the desired effect; too slowly, and the risk of bleeding increases. Levels of the drug in the blood are therefore typically monitored for weeks at the start of treatment, and drug dosages are adjusted accordingly — a process that requires repeated visits to a clinic. Because variants of two genes have large effects on the rate at which warfarin is metabolized, it was widely expected that clinical trials would show that warfarin dosing is improved by screening

for patients' genotypes. But trials showed that genetic screening led to no improvement in drug dosing.

Even here, however, some promise remains. A later trial led by Pirmohamed found a small but significant improvement when factors beyond genetics, such as the patient's age, body mass and other drugs they were taking, were considered. Using genetic information in combination with other factors may be better than using it in isolation. "I think there is promise in pharmacogenetics," says Evans, "but it's not going to revolutionize everything we do."

Pirmohamed is now part of a team that has secured US\$17 million from the European Union's Horizon 2020 funding programme to run the sort of large, randomized control trial that people want to see. Ubiquitous Pharmacogenomics will spend 3 years studying the clinical outcomes of 8,000 patients in 7 hospitals in 7 European countries. The trial will use a panel of 13 genes, and patients will be randomly assigned to groups that either do or do not receive pharmacogenetics-led prescription of drugs affected by those genes.

Proponents of pharmacogenetics stress that the outcomes of such trials are not the only results that should influence medical practice. Positive results have been seen in observational studies at hospitals such as St Jude that have nascent pharmacogenetics programmes, and Pirmohamed thinks that data from the UK 100,000 Genomes Project will also strengthen the case for clinical pharmacogenetics.

Relling is confident that pre-emptive clinical genotyping will one day be the norm. "We've had 50 years of research showing why it should be done," she says. But there is no doubt that the unambiguous results of a randomized clinical trial of *HLA-B* testing before prescribing abacavir to HIV patients in 2008 were pivotal to the test being widely adopted. So the upcoming Ubiquitous Pharmacogenomics trial, which begins next year and should report results in 2020, may have an important role in the future of personalized prescribing.

For Shelley Saunders, whose son Jason is part of St Jude's PG4Kids scheme, clinical pharmacogenetics seems to be ready for prime time. The choice to enrol in the programme was "one of the easier decisions we had to make", she says. "I don't know why anyone wouldn't want this."

But as physicians Evans and Pirmohamed are well aware, patients' safety must not be jeopardized by the pursuit of an apparently good idea. As the evidence builds, the use of pharmacogenetics may well become a common sight in hospitals and pharmacies around the world. But medicine is inherently conservative, and solid data are required if clinical practice is to change. ■

Liam Drew is a science writer based in London, UK.