

Why the long wait for gene-specific drugs? Personalised medicine has been a long time coming, and now researchers are wising up to the realities

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A WOMAN with severe depression walks into her doctor's office. He plucks a hair from her head to test her DNA. Later that day, after scanning the results, he prescribes the antidepressant drug that should work best for her. So began a New Scientist feature from 1998, which continued: "Patients could soon be taking drugs tailored to their genetic make-up, saving time and bundles of money now wasted on ineffective treatments, as well as minimising debilitating side effects" (14 November 1998, p 32).

Almost a decade later, this vision of personalised medicine has yet to become reality. People with hard-to-treat diseases like depression are still being prescribed drugs by trial and error. Adverse drug reactions are still one of the leading causes of death in the developed world. "It appears to have moved more slowly than we hoped," admits Richard Weinshilboum, a pharmacogeneticist at the Mayo Clinic in Rochester, Minnesota.

In part, the blame lies with pharmaceutical companies. They are still dominated by a one-size-fits-all mindset: trying to sell blockbuster drugs to as many patients as possible, regardless of their genetic make-up.

Pharmacogeneticists have also realised that biological sophistication alone will not win the healthcare industry over. If they are to move the idea of personalised medicine into the clinic they must also prove that genetically targeted drugs can lead to better and cheaper healthcare.

Having wised up to the economic realities, pharmacogeneticists are becoming more optimistic about the future. They are encouraged by signals coming from the world's leading drugs regulator, the US Food and Drug Administration (FDA). In August it announced plans to change the labelling of the anti-clotting drug warfarin to explain that variations in two genes, CYP2C9 and VKORC1, affect the way people metabolise the drug, and hence the doses they may need.

This is not the first time the FDA has ordered a change in drug labelling to mention a genetic test, but previous rulings have affected relatively small numbers of patients. By contrast, some 2 million Americans are put on warfarin each year – and excessive bleeding caused by the drug accounts for as many as 43,000 hospital emergency room visits. "It's not a niche drug," says Munir Pirmohamed, a pharmacologist at the University of Liverpool, UK. A session on warfarin was included in a pharmacogenomics meeting at Hinxton, in Cambridgeshire, UK, last week, which Pirmohamed helped organise.

The warfarin case also reveals how much further pharmacogeneticists must go before their work becomes mainstream. Even though the links between CYP2C9 and VKORC1 and patients' metabolism of the drug are well known, there is still little information on whether calculating dosage on the basis of genetics achieves better results than the conventional approach, which involves adjusting the dose over time in response to tests of the blood's clotting ability. "We need better clinical evidence," stresses Janet Woodcock, deputy commissioner of the FDA. Without firm evidence that genetic testing can improve drug safety, the FDA cannot require doctors to run genetic tests.

Doctors also want simple online tools into which they can plug the results of genetic tests – along with information such as patients' weight and their other medications – to obtain a firm dosing recommendation. A website called WarfarinDosing.org, developed by Brian Gage of Washington University School of Medicine in St Louis, Missouri, does provide this service. But at last week's meeting, researchers agreed that more effort is needed to determine how to calculate doses for populations across the world, which may respond differently to warfarin because of their different genetics.

As well as making life easier for doctors, pharmacogeneticists need to convince the managers and insurers who control the purse strings of medicine. Above all, that means showing that personalised medicine is cost-effective. "Before, our assumption was that it was just about the science. We thought: if

we build it, they will come," says Howard McLeod, a pharmacogeneticist at the University of North Carolina at Chapel Hill. "That was incredibly naive."

McLeod and others are now adopting a more cost-conscious approach: their latest studies include measurements such as whether genetic testing reduces the number of expensive follow-up visits to a doctor's office. "Warfarin costs pennies per pill to make, but thousands of dollars per patient to manage," McLeod says. The tests for CYP2C9 and VKORC1 cost a few hundred dollars per patient, but if they streamline management of patients on the drugs they could save money overall.

Perhaps the biggest economic players, however, are the drug companies, and they have a clear reason to be suspicious of anything that could limit the number of people to whom a new drug can be sold. "They don't have a big interest in fragmenting the market, and pharmacogenetics will fragment the market," observes James Evans of the University of North Carolina at Chapel Hill, editor-in-chief of *Genetics in Medicine*.

Enthusiasts for personalised medicine argue that this may change when companies see that a pharmacogenetic approach can "rescue" drugs that would otherwise have failed late in clinical testing, leaving a company with no return on hundreds of millions of dollars of investment. One example, a beta blocker for heart failure called bucindolol, could be approved by the FDA next year. Even more influential could be moves by GlaxoSmithKline (GSK) to introduce its diabetes drug rosiglitazone, also known as Avandia, as a treatment for Alzheimer's disease. More than most other drug giants, GSK has embraced a pharmacogenomic approach – thanks in part to the influence of Allen Roses, an Alzheimer's specialist and the company's head of genetics until his retirement earlier this year. Under his direction, GSK has found that rosiglitazone seems to improve the mental function of Alzheimer's patients who do not carry a gene variant known as APOE4 – although the exact mechanism is unclear.

The drug is now in the final stages of clinical testing, and if all goes well GSK will apply for approval to market it in conjunction with a genetic test to select which patients will benefit. Given that an effective drug against Alzheimer's is likely to be highly profitable, the industry may then sit up and take notice. "Nothing supports a strategy like success," says Roses, now at Duke University in Durham, North Carolina. "When something sells, it gets support."

SIDEBAR The Lazarus drug

By Peter Aldhous

Bucindolol was dead and buried. In 1999, a clinical trial of this beta blocker involving 2700 patients was abandoned after the drug performed no better in the treatment of heart failure than a placebo.

That would have been that, but for the persistence of Michael Bristow of the University of Colorado at Denver and Health Sciences Center, and Stephen Liggett of the University of Maryland, Baltimore. As part of the trial, they were studying bucindolol's performance in people with different forms of the gene for a receptor that responds to noradrenalin and adrenalin, both of which increase heart rate. After much number-crunching, they found that the drug actually worked well for about half of the 1000 patients for whom they had genetic data – those who carried two copies of one common variant of the receptor gene. For them, bucindolol reduced hospitalisation and deaths by more than a third, the researchers revealed last year (*Proceedings of the National Academy of Sciences*, DOI: 10.1073/pnas.0509937103). "We realised that genetic targeting would turn the drug into a best-in-class for a certain population," says Bristow.

Still, getting bucindolol back on track proved a struggle. Bristow was chief science and medical officer for a company called Myogen, but it was too busy developing other drugs. "I could not get my own company interested in it," he says. "Finally they said: 'You're not going to let this go, so we will let you spin a company out.'"

Bristow's new firm, called **Arca Discovery** and based in Denver, aims to apply for permission from the US Food and Drug Administration early next year to market the drug in association with a genetic test. If the drug is approved, Bristow hopes it will inspire other companies to follow a pharmacogenetic path. "One of the reasons we're doing this is to set an example," he says.