

Pharmacogenetics: what are the ethical and economic implications?

Two recent continuing professional development articles (one in this issue on pp109–12) have introduced the fundamental concepts of genetics and pharmacogenetics. In this article, **Philippa Brice** and **Simon Sanderson** discuss some of the ethical and economic implications

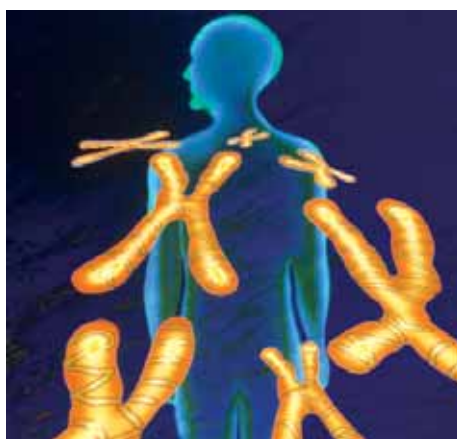
Advances in the understanding of the common genetic variants underlying drug response have created opportunities to develop new drugs and for assessing the suitability of patients for alternative drug regimens or dosages. However, these advances are accompanied by both ethical and economic implications.

Ethical implications

Regulators, drug companies, health care professionals and, increasingly, the general public are starting to realise that pharmacogenetics will have important ethical implications. Several organisations, most notably the Wellcome Trust and the Nuffield Council on Bioethics, have recently published influential assessments of the issues. Although many of the applications of pharmacogenetics are some way off, it is vital that advances in pharmacogenetic technology, its clinical applications and ethical guidance develop at similar rates.

Ethnicity One of the most recent (and controversial) developments in the pharmacogenetic field has been the marketing of BiDil for the treatment of heart failure in African-Americans. Hailed as the first “ethnic drug”, it is likely to be the first drug approved in the US for use in a single ethnic group. The US company NitroMed has claimed that racial differences in the response to heart failure treatment are due to underlying pathophysiological differences between ethnic groups. However, there has been considerable criticism of this approach, based primarily on whether race or ethnicity can be used as adequate markers of genetic differences and that this decision provides support for the concept of race as a distinct biological marker, with a risk of genetic discrimination.

Although there are genetic differences between racial and ethnic groups, these differences do not correlate well with factors, such as skin colour, that are often used to define them. Most research has reported that genetic differences between ethnic groups are much smaller than the variation within eth-



BSP/VE/Science Photo Library

Pharmacogenetic advances are accompanied by ethical and economic implications

nic groups. Classification by skin colour, race or ethnic group is a poor proxy for measuring common ancestry by pedigrees or genetic markers. This conclusion has been strengthened by recently published evidence, based on an analysis of a huge number of studies, demonstrating that gene variants have similar effects across traditionally defined racial groups. Ethnicity and race are poor markers of genetic make-up and should not be used to stratify drug development. Finally, by focusing on genetic causes for differential treatment response, other factors, such as lifestyle and socioeconomic status, may be neglected.

Drug stratification and orphan drugs

The ability to stratify patients into treatment groups on the basis of their genotype could lead to drug companies focusing on developing drugs for “easy-to-treat” patients, ignoring those with unfavourable or unusual genotypes or patients with rare diseases. Although this is a potential risk, others have argued that drug companies are more interested in developing multiple compounds to treat most population subgroups. From an economic perspective this makes more sense, as demonstrated by the problem of orphan drugs. The term “orphan drug” is used to describe drugs designed to treat people with rare diseases, including many genetic disorders. Legislation introduced in the US (1983) and Europe (2000) aimed to encourage research and development into such drugs by providing incentives and extended periods of market exclusivity. However, this niche market still remains unattractive and unprofitable for most of the major pharmaceutical compa-

nies, leaving small and innovative companies to fill the gap. Some have raised concerns that pharmacogenetics may exacerbate the orphan drug problem, where potentially valuable drugs are not developed because they would not have a large enough market, thus denying treatment to certain groups. The orphan drug question will continue to be an important policy issue with considerable ethical implications for the equitable provision of health care.

Pharmacogenetic tests There are also concerns that access to the necessary pharmacogenetic tests will be unequal, particularly for patients from poorer backgrounds or different ethnic or racial groups. In addition, some individuals may refuse to take a pharmacogenetic test.

It has also been suggested that patients may be excluded from treatment solely on the basis of test results whereas the assessment of the most suitable treatment should take into account a full range of factors including genetic and environmental influences. Although these fears are real, it must be borne in mind that patient stratification is part and parcel of normal clinical practice: it does not matter if this stratification is done on the basis of clinical features, an x-ray or a genetic test. If a drug is not indicated on the basis of its profile (which in the future may include genetic information) and the patient's condition, then it should not be prescribed.

In some instances, certain pharmacogenetic test results might also predict future risk of disease as well as drug response. For example, people with the slow metabolism variant of N-acetyltransferase 2 (NAT2) gene variants associated with slow metabolism are at risk of isoniazid-induced peripheral neuropathy and an increased risk of bladder cancer. Similarly, the apolipoprotein E4 (APOE4) gene variant is associated with a reduced response to statins and an increased risk of Alzheimer's disease.

Privacy and confidentiality Pharmacogenetic testing might reveal information that would be relevant to family members. This raises fundamental questions about how informed consent for testing is obtained and how test results should be communicated to patients, with implications for the provision of genetic counselling. This is a major concern, given the poor state of genetics knowledge among most health care practitioners.

Others are concerned about the privacy and confidentiality of stored genetic informa-

Philippa Brice, PhD, is science policy and dissemination manager for the Public Health Genetics Unit (part of the Cambridge Genetics Knowledge Park) and **Simon Sanderson, DPH, FFPHM**, is clinical lecturer in primary care genetics in the Department of Public Health and Primary Care, University of Cambridge and public health physician at the Public Health Genetics Unit

CYP2C9 gene variants and warfarin: an open and shut case?

A number of polymorphisms in the cytochrome P450 CYP2C9 gene determine the rate of warfarin metabolism. Patients homozygous for the CYP2C9*3 allele are slow warfarin metabolisers and are extremely sensitive to its effects, requiring much lower maintenance doses. These people are potentially at an increased risk of bleeding during treatment. So how could a genetic test be used? Given that the prescribing and monitoring of warfarin therapy is now conducted to such a high standard, using patient nomograms during initiation, close monitoring of the international normalised ratio and computerised decision support systems, bleeding events are now rare. Genotyping patients who are on stable warfarin doses is probably unnecessary because they can be managed on the basis of their anticoagulation tests and clinical features.

Genetic testing may be advantageous in two situations: deciding whether to use warfarin or an alternative anticoagulant or antithrombotic agent (such as aspirin) for elective treatment (such as for non-rheumatic atrial fibrillation) or by identifying patients who might be especially vulnerable during initiation. However, the predictive value of the genetic test for risk of bleeding is unknown, so it may not add much to standard management.

Finally, new drugs, such as direct thrombin inhibitors, which do not require intensive monitoring, will soon supersede warfarin. Using these new drugs may be more cost-effective than using a test-and-treat strategy for warfarin. Careful evaluation of these complex clinical decisions is, therefore, required before pharmacogenetic testing can be used in clinical practice.

tion and who will have access to it. There is a risk that insurers and employers might seek access to test results, although there are moratoria on the use of genetic test results by the insurance industry and a number of countries (eg, the US and Switzerland) are developing anti-genetic discrimination laws. It is vital that the public can have confidence that their personal information will be secure.

Economic implications

Around 30 large pharmaceutical companies are currently investing in pharmacogenetics, with GlaxoSmithKline, Roche and Pfizer being the main players. Their primary interest in pharmacogenetics is improving their efficiency in new drug discovery and development. Some have expressed concern that the "streamlining" of clinical trials for new drugs (by excluding patients with particular genotypes) could lead to increased adverse drug reactions once a drug is marketed because it will only have been tested in a small samples of subjects. However, it is likely that companies would be more interested in identifying any potential ADRs, given the huge financial

implications of product withdrawal. From a pharmacogenetics perspective, drug companies appear to be less interested in currently licensed drugs, except where value can be added through extending product licences, as has happened with the anti-HIV drug abacavir. Around 5 per cent of patients have a serious hypersensitivity reaction to this drug, which means that they must discontinue its use. However, the recent availability of a genetic test for hypersensitivity may substantially reduce this risk, meaning that abacavir can continue to be marketed. Given that development costs for a new drug are around \$1bn, the costs of genetic analysis are small (and falling all the time), making pharmacogenetics-based approaches even more attractive.

While there is a risk of market segmentation (production of drugs exclusively for use in genetically defined patient groups), most companies appear to be interested in developing drugs that are effective and safe in all population subgroups — developing products for larger rather than smaller markets makes better economic sense.

Pharmacogenetics could help in salvaging drugs that seem to be ineffective in a general patient population, but work in a smaller subgroup. However, it is unlikely that drugs withdrawn for safety reasons will be resurrected with an accompanying test for ADRs. This is because most of these drugs will be off patent (and so not financially attractive) and the appropriate genetic data required to develop suitable tests would not be available.

Some commentators have expressed concern that pharmacogenetics will increase the complexity of health care delivery and decision-making processes. One of the most important issues is whether pharmacogenetic testing will be more effective or cost-effective than patient monitoring (clinically or using alternative biomarkers). The Panel sets out some of the problems, using warfarin as an example.

There are also a number of key issues about who will initiate testing, who will communicate results to patients and who will be responsible for the quality of tests and overseeing the testing process, and its implications for treatment. These issues are likely to have an effect on primary care practitioners, including nurses and pharmacists.

There are already examples of pharmacogenetic tests available online and on the high street, thus enabling patients to access testing kits directly and perform the tests at home. For example, Sciona directly markets a number of genetic tests to consumers related to bone and heart health, insulin resistance and inflammation. Although such tests may accurately and reliably measure their included genetic variants, such sales are not regulated and there is no guarantee that the manufacturer has adequately validated them. There are also serious ethical and clinical issues at stake: there is little guidance or advice about the appropriateness of testing and the interpretation and implications of the results for the person concerned. There is little evidence to suggest

that genetic tests results improve health behaviour and motivation to change, but there is evidence that test results can lead to fatalism in those who test positive and a sense of invulnerability in those who test negative.

It is conceivable that similar testing kits may also be sold directly to patients through pharmacies; it is important to ensure that pharmacists understand the implications of testing and can advise patients on their suitability. However, it is not yet clear how such developments will be controlled and regulated, and who will regulate them.

The NHS Given that the annual drugs bill of the NHS is around £11bn, it is hoped that pharmacogenetics may benefit health care providers by enabling more effective, targeted prescribing, optimising the use of drugs, minimising waste and reducing the medical and financial impact of ADRs (for example, through reduced hospital stays). Although the NHS would need to finance the genetic tests, their costs are falling all the time and these would be small compared with the cost of drugs or ADRs. Nevertheless, the NHS must ensure that pharmacogenetic tests are rigorously evaluated before they are introduced into routine clinical practice, with clear evidence of clinical and cost effectiveness. The NHS has recently introduced a clear process (known as the Gene Dossier) for evaluating new genetic tests for clinical use, which includes pharmacogenetic tests.

Conclusion

Pharmacogenetics offers one of the earliest potential clinical applications of the "genetics revolution" although it will be some time before practising clinicians and pharmacists will be routinely using genetic information in their daily work. Most of the early benefits will be in the discovery and development of new drugs, with improvements in their efficacy and safety being the most tangible effects. However, considerable investment will be required in the evaluation of the effectiveness and cost-effectiveness of these strategies in drug use and in the education of health care practitioners. Policy makers and regulators will also need to think carefully about the ethical, legal and social issues that pharmacogenetics (including testing) raises and its implications for public policy and safety.

Further reading

- Rahemtulla T, Bhopal R. Pharmacogenetics and ethnically targeted therapies. *BMJ* 2005;330:1036–7.
- Roses A. Pharmacogenetics and drug development: the path to safer and more effective drugs. *Nature Reviews Genetics*. 2004;5:645–56.
- Breckenridge A, Lindpaintner K, Lipton P, McLeod H, Rothstein M, Wallace H. Pharmacogenetics: ethical problems and solutions. *Nature Reviews Genetics* 2004;5:676–80.
- Webster A, Martin P, Lewis G, Smart A. Integrating pharmacogenetics into society: in search of a model. *Nature Reviews Genetics* 2004;5:663–9
- Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. Available at www.nuffieldbioethics.org (accessed 17 May 2006).