

# Pharmacogenetics

## — current applications

By Jessica Clemerson, MRPharmS, and Katherine Payne, PhD, MRPharmS

Pharmacogenetics is already starting to impact on modern healthcare. The safety and effectiveness of several drugs can be improved by using genetic profiling. This article discusses how far pharmacogenetic testing has come towards being used in routine clinical practice



Hospital laboratories must detect overexpression of HER2 in the DNA of breast cancer tumour cells before the patient can be prescribed trastuzumab

**P**harmacogenetics explores the role of the single nucleotide polymorphisms (SNPs) (see Panel 1, p160) in the genes that encode drug metabolising enzymes, drug receptors, drug transporters and other proteins involved in the pathogenesis of a disease in determining a patient's response to a drug. It also describes the identification of the genetic make-up of tumour cells.

Although pharmacogenetic testing is still in early development, there is evidence that the safety and effectiveness of some drugs can be improved by pharmacogenetic testing. Such drugs include:

- Trastuzumab
- Thiopurines
- Irinotecan
- Abacavir
- Warfarin
- Tamoxifen

### — Trastuzumab

Trastuzumab is a recombinant humanised monoclonal antibody licensed for the

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treatment of breast cancer. It is only recommended for patients who have tumours that overexpress human epidermal growth factor receptor 2 (HER2) — the protein that is targeted by the drug.

Trastuzumab was heralded as one of the first clinical applications of pharmacogenetic testing, because the overexpression of HER2 must be confirmed before treatment can be started (the level of HER2 expression is determined from the DNA of tumour cells). Some controversy surrounds this classification, since the test examines tumour cell DNA, which may be significantly different from a patient's normal DNA and is not inheritable.

The National Institute for Health and Clinical Excellence has highlighted the need for HER2 testing before treatment with trastuzumab. Hospital laboratories provide this service within the NHS.

### — Thiopurines

The immunomodulating drug 6-mercaptopurine and its prodrug azathioprine are commonly used to treat acute lymphoblastic leukaemia and chronic inflammatory conditions (eg, rheumatoid arthritis, inflammatory bowel disease), and to prevent organ rejection following a transplant. However, the use of these drugs is associated with potentially serious side effects, such as profound neutropenia, which can be life-threatening. Therapeutic failure is also common. There is

an individual variation in toxicity and efficacy. Achieving a balance between the two is essential and requires carefully tailored treatment and monitoring.<sup>1</sup>

Azathioprine and 6-mercaptopurine are converted to their active metabolites by a series of enzymes, one of which is thiopurine methyltransferase (TPMT). Genetically determined variations in the activity of TPMT can lead to differences in drug toxicity and response. Low or absent TPMT activity has been shown to be associated with a risk of acute, profound neutropenia when the patient is exposed to standard doses of azathioprine.

Patients who are homozygous (explained in Panel 1 of the previous article, p160) for a mutant allele of the TPMT gene have low or absent enzyme activity. This accounts for 0.3 per cent of the population.<sup>2</sup> A further 10 per cent of the population is heterozygous for the mutant allele of TPMT and has intermediate activity of the enzyme. The remainder have two normal TPMT genes and therefore normal TPMT activity.

Measuring red blood cell TPMT activity (phenotyping) or DNA-based testing (genotyping) can help clinicians to identify patients who are at risk of toxicity from 6-mercaptopurine and azathioprine. Progress in establishing TPMT testing into routine clinical practice occurred in 2004 when the US Food and Drug Administration approved a change to the labelling of products that contain 6-mercaptopurine.

The label now highlights that TPMT testing can reduce the incidence of severe toxic events. Although testing was not made compulsory, the FDA decided that there was sufficient benefit in informing prescribers, pharmacists and patients of the availability of such tests, and the possible role that testing could have in the prescribing of this anti-cancer agent.<sup>3</sup>

The British National Formulary draws attention to the relationship between TPMT activity and response to azathioprine. Although there is no statutory requirement to test TPMT activity in the UK, the Department of Health is currently reviewing its advice on this issue.

**Phenotyping** Clinically accredited laboratories in the UK have developed assays to measure TPMT red blood cell activity and offer this service to clinicians. A recent survey conducted by Fargher *et al* reported that two-thirds of the consultants surveyed (dermatologists, gastroenterologists and rheumatologists) use TPMT level testing before prescribing azathioprine.<sup>4</sup> Higher uptake was seen in dermatologists, which reflects national dermatology guidelines that advocate the use of TPMT testing for patients who are to be prescribed azathioprine.

However, some clinicians remain sceptical about the added value of such testing compared with standard monitoring practices. In addition, the labour intensive assays required to conduct tests, the potential for laboratory-related variability and the fact that results can be affected by con-

comitant medication or previous blood transfusions are disadvantages of this method.<sup>5</sup>

**Genotyping** Currently, genotyping is not available for use in routine clinical practice. A trial funded by the Department of Health is currently investigating the cost-effectiveness and practical application for TPMT genotyping to inform the prescribing of azathioprine.

### Irinotecan

The topoisomerase I inhibitor irinotecan is used to treat colorectal cancer, although it can cause severe and potentially fatal diarrhoea and neutropenia. Its toxicity is caused by the active metabolite SN-38, which is further metabolised in the liver to the inactive metabolite SN-38 glucuronide (SN-38G).

There is considerable variation in the extent of this inactivation due to the variable expression of the gene that encodes the glucuronidating enzyme (UGT1A1). Clinical studies have detected a link between common polymorphisms of UGT1A1 and the risk of severe diarrhoea and neutropenia.

A genetic test has been made available to inform prescribing and, in 2004, the FDA approved a modification to the drug's labelling to indicate the role of testing in identifying UGT1A1 polymorphisms to reduce the risk of severe side effects. Since clear recommendations on the optimal use of the test are not available and the correlation between genotype and clinical outcome is not yet proven, it is not routinely applied in clinical practice but can be used at a doctor's discretion.<sup>6</sup>

### Abacavir

Abacavir has an established place in the treatment of human immunodeficiency virus (HIV). However, its use is associated with hypersensitivity reactions that cause fever, rash, abdominal complaints, lethargy and acute respiratory symptoms. Such reactions occur in approximately 4 to 8 per cent of patients.<sup>7</sup>

Studies have shown that possession of human leucocyte antigen (HLA) B\*5701 is a highly predictive genetic risk factor for abacavir hypersensitivity. This led to the proposal that genotyping for HLA B\*5701 could be performed before abacavir treatment is started. Therefore, those patients

who are positive for the antigen can be prescribed an alternative antiretroviral drug.

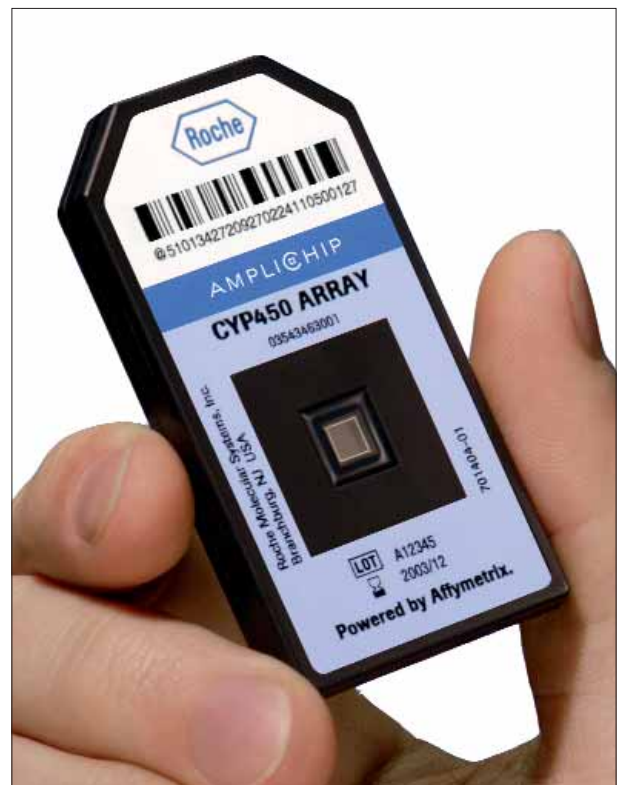
Some evidence suggests that such testing is cost-effective, so this is now routinely carried out in clinical practice in the UK.<sup>8</sup>

### Warfarin

Warfarin is the most commonly prescribed anticoagulant in the world. In the UK, it is estimated that at least 1 per cent of the total population and 8 per cent of those aged over 80 years are prescribed warfarin. Poor control of anticoagulation with warfarin is associated with significant risks to patients.<sup>9</sup>

Studies have shown that SNPs in the 2C9 isoform of cytochrome P450 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) make significant contributions to the variability in warfarin dosage. The combination of age and body surface area, together with genetic polymorphisms in CYP2C9 and VKORC1, accounts for 55 per cent of the variance in dose requirements.<sup>10</sup>

A prospective, non-randomised trial, funded by the DoH, is currently investigating whether this knowledge can be used to improve the safety of warfarin prescribing. This has the potential to herald a new era, in which warfarin dosing and hence INR control can be predicted better through the development of algorithms that consider both environmental and genetic factors.



The Amplichip CYP450 identifies a patient's ability to metabolise certain drugs by detecting polymorphisms in the CYP2D6 and CYP2C19 genes

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## Pharmacogenetics on the high street

The NicoTest is a prognostic test that offers patients who are attempting to quit smoking a personalised treatment regimen.

Individual variation in the rate at which smokers metabolise nicotine contributes to their response to nicotine replacement therapy. The unpredictability of this response may be partially attributed to genetic variation, such as CYP2D6 polymorphisms.

After purchasing the test kit, patients complete a questionnaire and return it to the manufacturer with a buccal swab. After analysis of the resulting genetic information, a personalised treatment regimen is recommended.

The manufacturer is undertaking a trial in several community pharmacies across Essex and London, and says the early results show patient outcomes to be significantly improved by using the test.

The test costs about £150 and is currently paid for by the patient.

## — Tamoxifen

The prescribing practice for tamoxifen, an oestrogen receptor antagonist licensed for the treatment of oestrogen-receptor positive breast cancer, may be altered by the use of CYP profiling (see below). Tamoxifen is a prodrug, metabolised by CYP2D6 to its more potent metabolite endoxifen.

Poor metabolisers of tamoxifen achieve lower levels of endoxifen than extensive metabolisers, and this may affect the drug's clinical outcome. One study has shown that poor metabolisers suffered earlier relapses of breast cancer compared with extensive metabolisers.<sup>11</sup>

CYP2D6 genotyping may provide rationale for prescribing alternative treatment regimens for some patients.

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## — CYP profiling

The CYP enzyme system consists of over 150 isoforms that are involved in the synthesis or breakdown of endogenous compounds (eg, corticosteroids, cholesterol and vitamins) and exogenous chemicals (eg, drugs). There are over 100 CYP genes that control the expression of these enzymes. Polymorphism within these genes can increase, decrease or abolish metabolism of certain drugs, therefore contributing to the variability in patient drug response. Over half of the commonly used drugs are cleared from the bloodstream through the action of these enzymes, with CYP2D6, CYP2C9, CYP3A4 and CYP2C19 being particularly significant.

**Amplichip CYP450** The Amplichip CYP450 enables polymorphisms in the CYP2D6 and CYP2C19 genes to be identified. Although other companies now offer clinicians the opportunity to genotype patients for polymorphisms in these genes, the Amplichip was the first genetic testing device to obtain approval from the FDA (which it received in 2004), and has also been approved for use across Europe. Genetic variations in the genes that encode

CYP2D6 and CYP2C19 result in four main levels of activity. By identifying polymorphisms in these genes, the Amplichip can determine whether an individual's ability to metabolise drugs using these enzymes is:

- Poor
- Intermediate
- Extensive
- Ultrarapid

Poor metabolisers will have difficulty inactivating certain drugs and eliminating them from the body, so are generally at increased risk of experiencing adverse drug reactions (ADRs). Conversely, ultrarapid metabolisers have an increased risk of being a non-responder because they can inactivate and eliminate a drug before it has produced a therapeutic effect. In the case of prodrugs, where enzymatic action is required before a therapeutic effect is achieved, ultrarapid metabolisers are at greatest risk of experiencing ADRs.

However, it should be remembered that genetic factors are not the only regulators of CYP activity. Other factors, such as concomitant drugs and diet, can also inhibit or induce CYP enzymes.

Since the regulatory approval of the Amplichip, a discourse has emerged around

how it can be applied in clinical practice to bring improvements to patient care. More research is required to create an evidence-based, cost-effective, genotype-guided use for this technology that can be applied in clinical practice.<sup>12</sup>

## — Getting the right evidence

Although pharmacogenetics could lead to more effective and timely treatment, this benefit might be a considerable burden on NHS resources. Robust clinical and economic evidence on the impact of pharmacogenetic technologies will be needed to inform local and national decision-makers.

Manufacturers of drugs must produce quality, safety and efficacy information (and in some cases, evidence of clinical and cost-effectiveness may also be required by NICE) before a drug can be recommended for use by the NHS. The approval process for pharmacogenetic tests is not so rigorous, so tests could emerge into clinical practice without sufficient supportive evidence.

Some tests are currently undergoing clinical evaluation and others have already been evaluated for cost-effectiveness (eg, TPMT tests). Such studies have suggested that the tests are good value for money, but caution

is advised in interpreting their results because many have made assumptions about a test's ability to predict a side effect. Further work is necessary to provide robust clinical and economic evidence to help decide whether to add pharmacogenetic tests into prescribing practices.

## — Conclusion

It is clear from the examples above that pharmacists working in areas such as oncology or HIV treatment are likely to see pharmacogenetic testing playing an increasingly important role within their specialties in the near future. In addition, pharmacogenetic testing may begin to inform the prescribing of some commonly used drugs, such as warfarin and azathioprine.

Although developments in the understanding of pharmacogenetics could change clinical practice in defined areas in the short term, other clinical areas may not see any impact for many years, if at all. It is certain that genetic factors contribute to the uptake, distribution, metabolism and effect of many medicines, however pharmacogenetic testing is only likely to be clinically useful for a relatively small number of them. Even in those medicines for which pharmacogenetic test-

ing can be helpful in making therapeutic decisions, such tests may have no added value compared with the approach used in current practice and are therefore not justifiable.

The view that pharmacogenetic testing could mean a complete departure from "trial and error" prescribing, and deliver personalised medicine (as has been proposed in both the lay and scientific literature), is not a valid one.

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*References on p173*

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## References

1. Panya B, Thomson w, Poulton K, Bruce I, Payne D, Qasim F. Azathioprine toxicity and thiopurine methyltransferase genotype in renal transplant patients. *Transplantation Proceedings* 2002;34:1642–5.
2. McLeod HL, Coulthard S, Thomas AE, Pritchard SC, King DS, Richards SM, et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. *British Journal of Haematology* 1999;105:696–700.
3. Maitland ML, Vasisht K, Ratain MJ. TPMT, UGT1a1 and DPYD genotyping to ensure safer cancer therapy? *Trends in Pharmaceutical Sciences* 2006;27:432–7.
4. Fargher EA, Tricker K, Newman W, Elliot R, Roberts SA, Shaffer JL, et al. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. *Journal of Clinical Pharmacy and Therapeutics* 2007;32:187–95.
5. Payne K, Newman W, Fargher E, Tricker K, Bruce IN, Ollier WER. TPMT testing in rheumatology: any better than routine monitoring? *Rheumatology* 2007;46:727–9.
6. Innocenti F, Ratain MJ. Pharmacogenetics of irinotecan: clinical perspectives on the utility of genotyping. *Pharmacogenomics* 2006;7:1211–21.
7. Peyriere H, Guillemin V, Lotthe A, Balliat V, Fabre J, Favier C. Reasons for early abacavir discontinuation in HIV-infected patients. *Annals of Pharmacotherapy* 2003;37:1392–7.
8. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B\*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 2004;14:335–42.
9. Kamali F, Pirmohamed M. The future prospects of pharmacogenetics in oral anticoagulation therapy. *British Journal of Clinical Pharmacology* 2006;61:746–51.
10. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 2005;106:2329–33.
11. Goetz MP, Knox SK, Samen VJ, Rae JM, Safgren SL, Ames MM, et al. The impact of CYP450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast cancer research and treatment* 2007;101:113–21.
12. Jain KK. Applications of Amplichip CYP450. *Molecular Diagnosis* 2005;9:119–27.

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