

Uses for genetics in pharmacy

It is likely that pharmacogenetics will be one of the earliest applications of genetic science in the post-genomic era. In a second article on genetics and medicines, **Philippa Brice** and **Simon Sanderson** look at current and future applications of pharmacogenetics in drug development and prescribing

Pharmacogenetics can be defined as the application of genetic analysis to predict drug response, efficacy and toxicity. More recently, since completion of the Human Genome Project, the term “pharmacogenomics” has come into common use (see Panel 1) but in this article, we will continue to use “pharmacogenetics”.

The discipline of pharmacogenetics dates back to the 1950s with the observation of variable inherited clinical responses to primaquine, isoniazid and the anaesthetic succinylcholine. Primaquine can cause haemolytic anaemia in those with glucose 6-phosphate dehydrogenase (G6PD) deficiency, isoniazid is likely to cause more severe side effects in people who are “slow drug metabolisers”, and patients with a defective metabolising enzyme experience prolonged muscle relaxation when succinylcholine is used. The DNA (deoxyribonucleic acid) sequences of the genes involved, however, have only recently been determined.

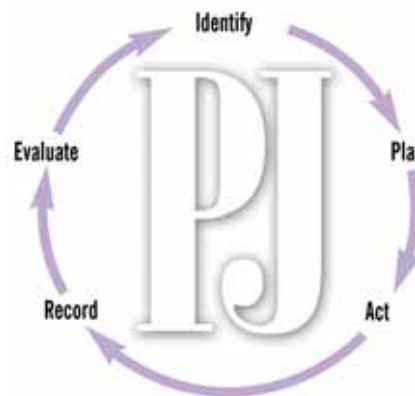


Pharmacogenetics is increasingly being used as part of drug development pipelines

Drug discovery and development

The discovery and development of new drugs is expensive and risky. Most fail in early clinical trials, with a failure rate of around 97–99 per cent being common. It typically takes 13 or 14 years to bring a new product to market, at a cost of around £550m. Pharmacogenetics could help to reduce high failure rates and development costs by identifying potential responders and non-responders to a drug at an early stage, using genetic variants that are markers of drug efficacy. Most of these variants are single nucleotide polymorphisms (see *PJ*, 8 July, p53), acting alone or in combination (haplotypes).

By identifying genetic markers that suggest how trial participants are likely to react to a drug candidate, a subgroup of potential good responders can be selected for subsequent later-stage clinical trials, helping to reduce their cost and to improve the success rate. For example, a group of individuals could be subgrouped according to their



Identify knowledge gaps

1. What is pharmacogenetics?
2. How might pharmacogenetic information be used in drug development?
3. Can you name a drug for which pre-prescription pharmacogenetic testing is currently available?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “effects of inter-patient variation on drug therapy” and “keeping abreast of issues affecting pharmacy”.

genotype for a common polymorphism in the multidrug transporter gene ABCB1 at position 3435. There are two alternatives, C or T, and individuals will be either CC, CT or TT with respect to this variant. Classification of patients by genotype may also allow particular gene variants to be identified that would have been missed if unselected groups of patients were used. For example, GlaxoSmithKline is now storing DNA from all participants in Phase IIA clinical trials so that genetic analyses can be conducted if drug efficacy is demonstrated in only part of the study population. Patients with different variants of drug metabolising enzymes (especially those belonging to the cytochrome P450 enzyme group) are now being included in trials so that the related differential treatment responses can be assessed at an early stage.

Pharmaceutical companies are increasingly using pharmacogenetics as part of their internal drug development pipelines. For example, pharmacodynamic markers (a surrogate measure of pharmacologic response, such as cortisol levels in the serum or urine) are used to screen novel corticosteroid compounds.

Panel 1: What's in a name?

Although the terms “pharmacogenetics” and “pharmacogenomics” are often used synonymously, there are subtle differences in their meaning. Pharmacogenetics essentially refers to how a person's genetic make-up influences their response to drugs and, in particular, how specific genes affect the responses to specific drugs or drug classes.

Pharmacogenomics is a somewhat broader term, referring to the genome-wide search for genes and associated products (such as enzymes or other proteins) that may be suitable targets for new drug discovery or that interact with other genes and environmental factors in determining drug response.

Examples of gene variants that influence drug response

Gene variant	Name	Drug response (phenotype)
<i>Pharmacodynamics</i>		
ADRB1	β_1 adrenergic receptor	Increased response to salbutamol
COX	Cyclo-oxygenase	Variable response to aspirin and other non-steroidal anti-inflammatory drugs. Individuals with extensive metaboliser COX variants require higher doses for therapeutic effect.
CETP	Cholesterol ester transfer protein	Increased response to atorvastatin and pravastatin.
HTR2A	Serotonin receptor 2A	Reduced response to clozapine.
<i>Pharmacokinetics: drug transporters</i>		
ABCB1	Drug transporter MDR1	Resistance to anti-epileptic agents (eg, phenytoin); increased immune recovery after starting anti-HIV drugs.
<i>Pharmacokinetics: metabolism</i>		
CYP2C19	Cytochrome p450 2C19	Decreased response to omeprazole.
CYP2D6	Cytochrome p450 2C9	Variable response to codeine. Individuals with extensive metaboliser CYP2D6 variants require higher doses for a therapeutic effect and those with poor metaboliser variants require lower doses to avoid side effects.
GSTM1	Glutathione S-transferase M1	Increased survival following chemotherapy for ovarian cancer.

Identification of compounds that produce pharmacodynamic profiles that differ from those of standard drugs or pro-inflammatory agents are of interest as candidate drugs with improved efficacy and safety profiles. Since the genetic basis of most responses to a drug is the product of multiple interacting genetic factors, involving variants in different genes involved in drug metabolism pathways, there is increasing interest in "pathway-based pharmacogenetics", looking at inter-individual variation in whole metabolic pathways as opposed to a specific key point in a given pathway. Already, drug candidates found to be metabolised by pathways known to be subject to significant pharmacogenetic variation can be excluded from further development in order to produce drugs that will be effective in all population subgroups.

Most drug targets are currently selected on the basis of disease pathophysiology but the completion of the Human Genome Project has energised the search for new drugs on the basis of newly determined gene sequences. The two main groups of genes that are important in understanding drug response and are, therefore, of interest, are:

- Those influencing the pharmacokinetic properties of drugs, such as genes responsible for drug metabolising enzymes and drug transporters
- Those influencing pharmacodynamic properties of drugs (eg, genes responsible for drug targets and their associated pathways)

The completion and widespread availability of both the human and mouse genome sequences means that many genes can be analysed *in silico* (the computerised analysis of on-line genome sequences) for target genes.

There are around 22,000 to 25,000 human genes in the human genome. Probably only around 1,800 currently known genes belong to possible drug target groups (such as nuclear receptors and kinases) but it will take time for functional gene variants and their proteins to be identified and for new drug molecules to be developed on this basis.

The identification of sub-groups of patients with specific polymorphisms or haplotypes may streamline the drug development process by directing development specifically for these groups. This approach has been termed "drug stratification" and has created some ethical concerns about who will benefit from new drug development approached (see **Article**, p113).

Prescribing

In the US, reference is now made to drug-metabolising enzyme genotypes in prescribing information for theophylline, celecoxib, aripiprazole, modafinil, thioridazine and atomoxetine. For example, the label for thioridazine states that it is contraindicated "in patients, comprising about 7 per cent of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6". It is not clear, however, whether or not prescribers are using this information in their day-to-day decisions.

Also in the US, prescribing guidance for a number of drugs (including imatinib, trastuzumab, somatropin, tretinoin for leukaemia and cetuximab) now includes information on the use of predictive pre-prescription genetic testing. These tests can be used to help prescribers identify potential responders (or non-responders), or those who are likely to suffer adverse drug reactions (ADRs), before treatment is initiated. Nevertheless, judgements about the clinical usefulness of pharmacogenetic tests are highly context-specific, depending on patient factors, their illness, treatment goals and the likely costs, benefits and harms of intervention — pharmacogenetically suitable patients (eg, responders) are not necessarily clinically suitable patients.

Currently, pre-prescription pharmacogenetic testing is largely limited to expensive drugs for conditions such as cancer, where use of an ineffective treatment would not only be costly, but could also have a significant impact on the survival prospects of the patient, for example, by delaying access to an effective alternative. For example, trastuzumab is licensed for the treatment of metastatic breast cancer in patients with tumours that over-express human epidermal growth factor receptor 2 and tumour cells are tested to identify patients for whom trastuzumab is a treatment option.

In theory, a test that could function as an efficient factor in determining the best choice of drug for a given patient and condition might also be useful for conditions such as depression or hypertension. Although the initial cost of the test would be high, its function in reducing the number of repeat visits to the

Reference to drug-metabolising enzyme genotypes is being given in prescribing information

clinician and months spent receiving ineffective medicines might compensate for this in terms of both patient experience and overall expenditure. However, the availability and timeliness of genetic tests is also a concern when decisions have to be made quickly — in some cases, performing a genetic test would take too long to be of any practical value to guide prescribing.

If efficacy-based pharmacogenetics is to make an important contribution to patient management, clear evidence linking specific genotypes to clinical outcomes in different populations will be needed, as well as clear guidance about the practical prescribing actions to be taken.

Personalised medicines Pharmacogenetics may provide a way of tailoring the prescribing to individual patients, based on their genetic make-up, with the aim of improving their safety, effectiveness and cost-effectiveness. Some have suggested that, in the future, patients will have “personal pharmacogenetic profiles” that will enable prescribers to use genotype-specific treatment guidelines. However, these developments are still a long way off: the Royal Society’s 2005 report on personalised medicines¹ concluded that pharmacogenetics was unlikely to revolutionise clinical practice in the near future and that its mainstream impacts were probably 15–20 years away. The major problem is that treatment responses, failures and the occurrence of ADRs are highly complex phenomena that cannot easily be reduced into categories based solely on the genetic data.

Pharmacogenetics is not a “magic bullet” that will solve all efficacy and safety problems. As our understanding of pharmacogenetic mechanisms increases, it will become increasingly possible to develop appropriate tests and drugs for certain diseases, disease subgroups and eventually patients but these will need to be properly evaluated in trials to assess their effectiveness and cost-effectiveness on a case-by-case basis. Ultimately, pharmacogenetics may also help stratify patients into groups defined by genotypes, providing an additional source of information to help prescribers make decisions.

Efficacy and safety

Drug response can vary by as much as 30-fold between individuals and some of this variability is genetically determined. Variants of genes can affect drug response. Examples of genes that are linked with response to drugs and their pharmaceutical impact are shown in the Table.

The prevention of ADRs is extremely important both for patient safety and for the cost-effective use of limited health care resources. In 2004, Pirmohamed *et al* published an analysis of the impact of ADRs on two large Merseyside NHS hospitals over six months. They found that 6.5 per cent of over 18,000 admissions were due to ADRs, and projected that the annual cost to the NHS was around £466m. Most of these events were thought avoidable, with the main culprits



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Some pharmaceutical companies are storing DNA from participants in clinical trials for genetic analyses

being low-dose aspirin, warfarin, other non-steroidal anti-inflammatory drugs and diuretics.² Another example is given by a study that investigated chemotherapy-induced toxicity in ovarian cancer. The study assessed the costs of the three most common ADRs: neurotoxicity, neutropenia and thrombocytopenia. Average costs per patient directly attributable to these problems were £390, £4,281 and £1,854, respectively. Indirect costs (eg, patients’ loss of earnings) were also found to be substantial.³ If these ADRs could be prevented, patients would have improved quality of life and the costs of treatment would be averted.

Pharmacogenetics may provide opportunities to improve drug safety, starting with the development of new drugs. As mentioned above, clinical trials for drugs in development can now be designed to include patients with certain genetically determined variants in specific drug-metabolising enzymes, some of which may be responsible for ADRs.

For example, during GlaxoSmithKline’s Phase III trials of the drug tranilast for the prevention of restenosis (now discontinued for efficacy reasons) 4 per cent of trial patients developed asymptomatic hyperbilirubinaemia, creating concerns about its future development and possible product licensing restrictions. Genetic analysis of genes with a potential role in metabolism of the drug found that this reaction was strongly associated with a variant in the uridine diphosphate glucuronyltransferase gene (a known cause of Gilbert’s Syndrome which also leads to asymptomatic hyperbilirubinaemia). Using a similar strategy, it would now be possible to use genetic analysis to help understand ADRs earlier in the development process, influencing decisions about whether or not to continue with drug development, or to target drug development to specific sub-groups (eg, anyone with Gilbert’s Syndrome would be excluded).

The late identification of serious ADRs post-launch has serious clinical implications for patients and can lead to product withdrawal. Pharmacogenetics may be able to assist in post-marketing surveillance by providing a mechanism for identifying patients at risk of serious and rare ADRs through the rapid development of a genetic test (as in the tranilast example).

Some researchers have proposed that DNA from the first 250,000 patients treated with a new drug should be collected and stored. If serious ADRs occur then this DNA could be used to identify associated genetic variants and to develop a predictive test. While this might seem attractive, there are a large number of practical difficulties with its implementation, including obtaining informed consent, ensuring the privacy and confidentiality of data. The question of funding for the DNA collection and its storage is another issue that could prove problematic.

A more practical approach for improving safety is pre-prescription testing to identify patients at risk of ADRs. The best clinical example of this approach is for the thiopurine drugs azathioprine and 6-mercaptopurines (see Panel 2). However, as demonstrated in this

Definitions

Genotype The specific genetic constitution of an individual.

Phenotype The observable traits of an organism, resulting from a combination of genetic and environmental factors.

Polymorphism Common variation in a region of DNA sequence among different individuals; the variation should be present in at least one or two per cent of the population to be considered a polymorphism.

Panel 2: Thiopurine S-methyltransferase and the thiopurines

Drugs such as 6-mercaptopurine, azathioprine and 6-thioguanine are widely used in oncology, dermatology and other specialist fields of medicine. These have a number of potentially serious side effects, including fatal myelosuppression. Metabolism of these drugs is performed primarily by the enzyme thiopurine S-methyltransferase (TPMT), although others are involved, including methylenetetrahydrofolate reductase. A number of common polymorphisms in the TPMT gene determine the level of enzyme activity. Individuals with low or intermediate activity are at risk of drug toxicity unless the drug dose is reduced, usually to about 10 per cent of standard doses.

Pre-treatment genetic testing has been carried out in the US for around 10 years now, and there is evidence to suggest that it is cost-effective in certain health care settings. One of the difficulties of transferring testing to other countries is that there are around 13 known alleles associated with reduced TPMT activity, first identified in predominantly Caucasian patients. However, these variants have different frequencies in different population groups as well as variation in functional effects between heterozygous and homozygous individuals, suggesting that other genetic or environmental factors have a role in determining drug response to these particular drugs.

example, the availability of a genetic test does not necessarily mean it is going to be useful in clinical practice because of the large number of non-genetic factors that influence drug response, such as comorbidities, comedication, nutritional status, compliance and so on. In addition, some hospital physicians prefer not to use available pre-prescription testing, because they believe that high levels of patient monitoring are as effective in the prevention of serious adverse reactions. Nevertheless, the capacity to predict drug efficacy in advance of treatment based on patient genotype is an area of particular interest within pharmacogenetic testing, since this would represent a major clinical advantage in treatment terms.

The potential economic benefits of pre-prescription pharmacogenetic testing need to be considered on a case-by-case basis for each pharmacogenetic test or drug combination. In particular, although the use of a test might allow the prescriber to determine whether or not a particular drug is suitable for use for a given patient and condition, would the benefits from avoiding ADRs or inefficacious drug use outweigh the costs of delivering the test?

Besides the cost of the test itself, a full health-economic analysis must allow for a range of variables including the likely ratio of drug responders to non-responders in a patient population, the likely incidence and costs of ADRs and the effectiveness and cost of the drug in question. Unless a test is cheap, the only situation in which testing is likely to be economically justifiable is where the proportion of non-responders in a population is high or the potential adverse reactions are significant, or both.

From a commercial perspective, the use of genetic testing that subdivides the patient population may make that drug financially non-viable. For this reason, it may be smaller diagnostic or biotechnology companies that produce pharmacogenetic test kits rather than the drug manufacturers themselves, whose primary interest in pharmacogenetics is as part of the internal drug development process.

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Conclusion

There is no doubt that pharmacogenetics will have an important role in improving the efficacy and safety of drugs in development and of those currently available. Although there are few current examples of the use of pharmacogenetics in practice, these will increase as our understanding of how genes influence drug response increases. However, genetics should not overshadow the critical non-genetic factors that also determine drug response, including age-related physiological decline in drug metabolism, diet and other lifestyle choices (eg, cigarette smoking), other illnesses, polypharmacy and drug interactions, as well as compliance with treatment. Greater understanding of how these genetic and environmental factors interact is required and the skills of prescribers and pharmacists will continue to be important contributors to a patient's drug response.

Translating knowledge of pharmacogenetics into clinical practice will remain an important obstacle to its successful implementation; clear evidence of clinical and cost-effectiveness will be needed if pharmacogenetics is to fulfil its promise.

References

1. The Royal Society. Personalised medicines: hopes and realities. 2005. Available at www.royalsoc.ac.uk (accessed 17 May 2006).
2. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
3. Wolf R, Smith G, Smith RL. Science, medicine and the future: pharmacogenetics. *BMJ* 2000;320:987-90.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. What drugs should be avoided in G6PD deficiency? Read section 9.1.5 in the British National Formulary.
2. Explore pharmacogenetic issues further. Read the **Article** on p113 about some of the ethical and economic implications of pharmacogenetics. Discuss these issues with a colleague.
3. Consider how would you explain the influence of genetic and environmental factors on health and drug response to a member of the public.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?