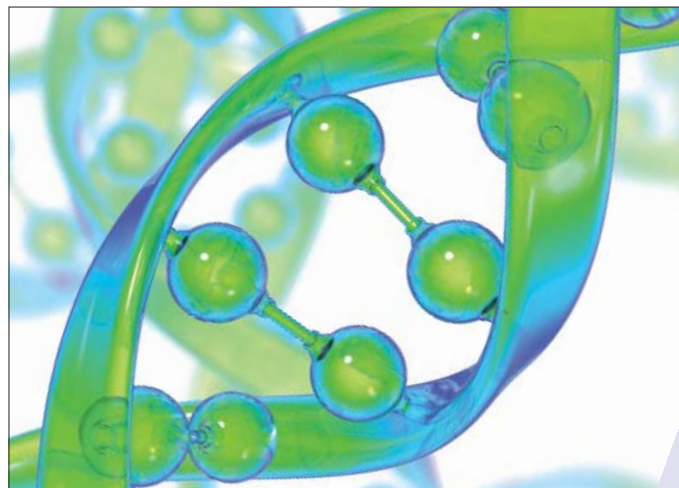


# Pharmacogenetics

## — background and future potential

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

Individual variation in response to drugs is a substantial clinical problem. Genetic makeup contributes to this variation. This article describes the underlying principles of pharmacogenetics and the potential of pharmacogenetic testing



Variations in DNA sequence are related to how patients respond to drugs

**V**ariation in drug response can result in therapy failure or adverse drug reactions (ADRs). The clinical consequences range from mild, self-limiting side effects to serious illness or death. In the UK and the rest of Europe, data have shown that around 7 per cent of hospital admissions are caused by ADRs.<sup>1</sup> In the US, ADRs occurring in hospital rank among the top six causes of death.<sup>2</sup>

Genetic factors are estimated to account for 20 to 95 per cent of interpatient variability.<sup>3</sup> Unlike other factors that influence drug response, inherited determinants that affect drug metabolising enzymes, drug receptors and drug transporters, remain stable throughout a patient's life.

### — The story so far

The term "pharmacogenetics" was first used in the 1950s to describe clinical observations of inherited differences in drug effects. It now describes the study of how interindividual variations in DNA sequence are related to drug response. The use of genetic markers in healthcare is not a new phenom-

enon, but has been used for years (eg, in organ transplant and blood transfusions).

The completion of the Human Genome Project (HGP) is one of the greatest scientific achievements of the past 50 years. This project, which was completed in 2003, identified the thousands of protein-coding genes in the human genome and sequenced the billions of chemical base pairs that make up human DNA.

An explanation of the basic terms used in pharmacogenetics can be found in Panel 1 (p160). Genetic make-up is broadly similar in humans, regardless of gender or ethnicity. However there are small variations in the genetic code, referred to as single nucleotide polymorphisms (SNPs) (see p160), which can have a profound effect on how an individual develops disease or responds to a medicine.

The HGP identified over 1.4 million SNPs, with at least 60,000 of them in the

coding regions of genes. Research in pharmacogenetics has gained momentum in recent years, fuelled by these findings. It is hoped that increased knowledge in this field will allow genetic information to be used to inform prescribing decisions and allow more accurate prediction of drug safety and efficacy in individual patients.

However, despite it being over 50 years since the conception of pharmacogenetics, most clinicians still prescribe on a "one drug fits all" basis.<sup>4</sup> The potential in this field is yet to be realised, but there are several current examples of how pharmacogenetic testing is improving patient care. The second part of this feature (p167) discusses these examples.

Some of the terms used by the pharmacogenetics industry are defined in Panel 2 (see p161). The application of pharmacogenetics falls broadly into two groups:

- Using genetic information to test for variation in an individual's germline DNA (the inherited genetic make-up of every cell in the body), which may, for example, determine the activity of a drug metabolising enzyme
- Analysing the DNA of tumour cells (this may be different from cells in the rest of the body and not inherited)

### — Mixed opinions

Scientists have suggested many utopian visions of what pharmacogenetics can

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**Jessica Clemerson** is senior lecturer in pharmacy practice at the University of Sunderland and practice pharmacist for the Falcon Medical Group, Newcastle-upon-Tyne. **Katherine Payne** is a senior research fellow in health economics at the University of Manchester.

deliver to clinical practice. Some say that, in the foreseeable future, pharmacogenetic research will lead to the development of drugs that are more cost-effective, and medicines that respond better to patients' needs.

Several stakeholders positively support pharmacogenetics and are attempting to drive forward scientific understanding and technological development in this area. These include the pharmaceutical industry, which is presented with the challenge of bringing new drugs into an increasingly competitive market. In addition, the Government faces mounting costs for delivering healthcare, so continues to look for solutions that improve the cost-effectiveness of pharmaceuticals.

Patient groups may also show an interest in pharmacogenetic developments if they offer improvement to the medicines selection process and result in improved drug efficacy and reduced ADRs.<sup>6</sup>

However, the scientific community has not been universally enthusiastic about the potential of pharmacogenetics. Experts have urged caution in light of unsubstantiated claims and calls have been made for a greater level of realism regarding the expectations of pharmacogenetic applications. This is primarily because, despite the significant progress in the mapping of the human genome, the connection between genotype and phenotype in drug response is complex. It is rare that one gene is responsible for a patient's response to a medicine. Usually, the inherited response is determined by the interplay of several genes, all of which encode proteins involved in multiple pathways of a drug's metabolism, disposition and effect.<sup>7</sup>

Outside the scientific community, the claims made for pharmacogenetic potential have not escaped scrutiny. Positive reports of

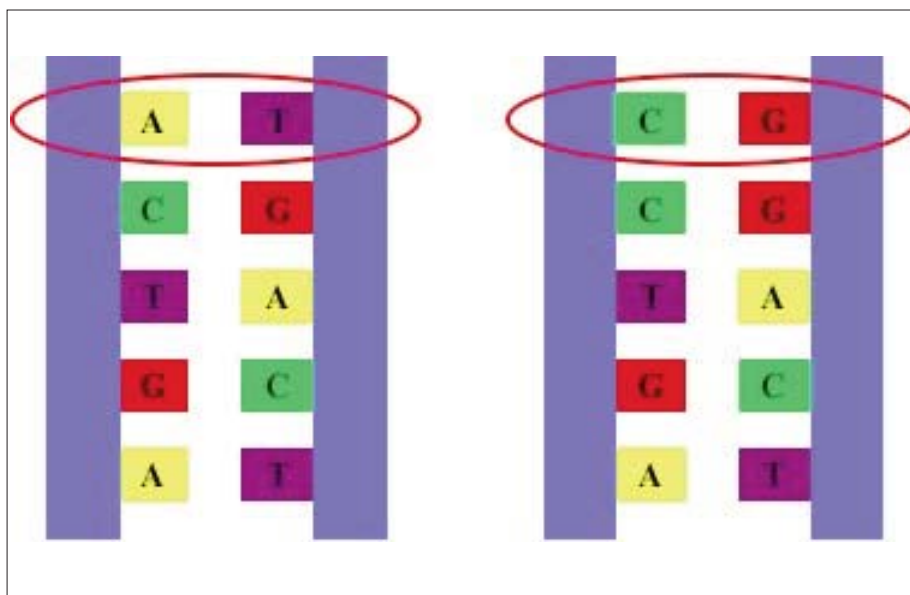


Figure 1: Two DNA strands that would have been identical, if not for the occurrence of a single nucleotide polymorphism at the first base pair

“personalised” medicine in the lay press have been tempered by bodies such as GeneWatch UK. Its report “Pharmacogenetics: better, safer medicines?” urges patients to understand the limitations of pharmacogenetics and not assume it will determine the medicine that each patient should receive.<sup>8</sup>

### Service delivery

One factor that is likely to be highly determinant in shaping pharmacogenetic services is the location at which testing can take place. Near-patient testing may become possible in the future if the technology becomes mobile and sufficiently cost-effective.

Currently, some pharmacogenetic tests are carried out by the NHS. For example,

thiopurine methyltransferase (TPMT) level testing can be performed to inform the prescribing of azathioprine (see p167). This requires blood samples to be sent to clinical laboratories and the results returned to the ordering clinician. The TPMT test is currently available from two NHS laboratories in England, both of which performed over 10,000 tests in 2006.

Additional factors can also influence pharmacogenetic service delivery, such as the level of interest from the pharmaceutical industry and arrangements for the funding of healthcare systems.

**Industry involvement** If a new drug developed by the pharmaceutical industry requires a pharmacogenetic test to be carried out before treatment is started, the cost of testing may be funded by the manufacturer. However, as illustrated in the testing of breast cancer for the presence of human epidermal growth factor receptor 2 (HER2) as a prerequisite to trastuzumab treatment, this may only be a temporary arrangement. HER2 testing was initially paid for by the manufacturer of the drug but it is now funded by the NHS.

**Health service structure** Differences in healthcare arrangements between countries will significantly affect the shaping of arrangements for pharmacogenetic testing in those countries. In the UK, pharmacogenetic testing is likely to be encompassed by the services provided by existing NHS reference laboratories. Some private companies also offer pharmacogenetic testing in the UK. One company, DxS Ltd, offers services to pharmaceutical companies, clinical research organisations and healthcare providers.

In the US, the private sector is likely to have a greater opportunity to offer pharma-

## Panel 1: A refresher in pharmacogenetics

A **gene** is a strand of DNA, in which nucleotides are contained in coding regions and non-coding regions. The sequence of nucleotides in a **coding region** denotes the amino acid sequence of a protein that is required for the cell to function. The sequence of nucleotides in a **non-coding region** may have little or no known function.

Occasionally, one of the nucleotides in a DNA sequence may change. This is known as a **single nucleotide polymorphism (SNP)**. If the SNP occurs in the coding region, this can lead to an alteration in the amino acid sequence of the encoded protein and, potentially, a protein with altered function. This can affect pharmacodynamic or pharmacokinetic processes.

All genes exist in two places in the body: at the same location on two homologous chromosomes. The two forms of the gene are known as **alleles**. If the two alleles are identical, the person is **homozygous** for that gene. If the two alleles differ, the person is **heterozygous** for that gene.

Organisms can be classified in two ways:

- By **genotype** — according to a genetic characteristic (eg, possesses the human leucocyte antigen B\*5701)
- By **phenotype** — according to a biological characteristic (eg, a poor metaboliser of a particular drug) that can be the result of genetic or environmental factors

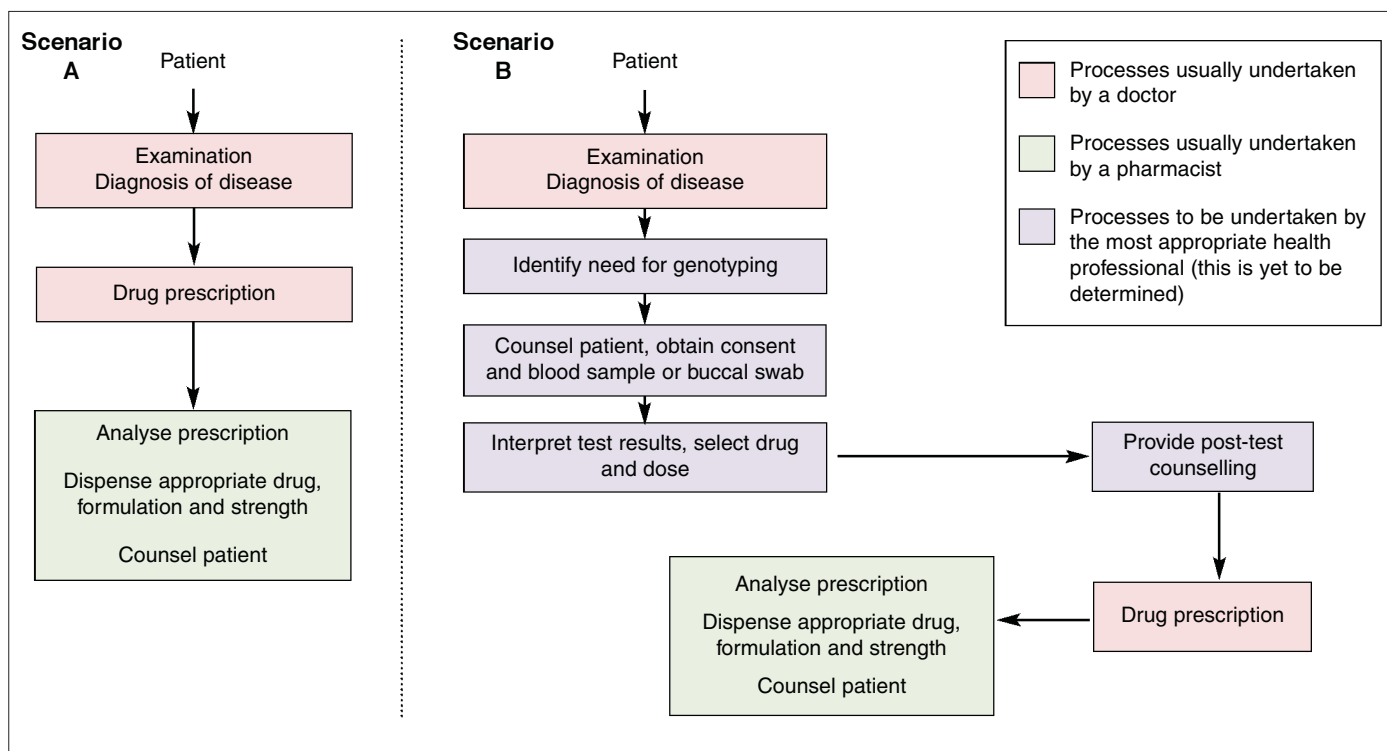


Figure 2: How the prescribing process may be altered by the introduction of pharmacogenetic technologies. Scenario A shows the processes that are undertaken currently for a patient to receive a prescription. Scenario B shows how the process may alter if pharmacogenetic testing becomes necessary

cogenetic testing to healthcare providers, because privately funded healthcare providers are more common.

### Role of the pharmacist

The introduction of pharmacogenetic testing could alter prescribing practice, as shown in Figure 2. In current practice (scenario A), a doctor examines the patient, makes a diagnosis and prescribes a medicine. Pharmacists ensure that the medicine has been prescribed appropriately. Occasionally, they may also be involved in making the prescribing decision, an

arrangement that will become more frequent as the numbers of pharmacist prescribers (both supplementary and independent) increase.

Pharmacogenetic testing has the potential to add several steps to this process, as shown in scenario B. Once a diagnosis has been made and the decision taken to start drug therapy, the prescriber will need to determine if pharmacogenetic testing would aid drug or dose selection. If so, informed consent and a blood sample or buccal swab will need to be obtained from the patient. In addition, test results will require interpretation to determine the

appropriate drug and dose, and the patient may need to be counselled about the implications of the result.

It is possible that pharmacists could be responsible for some or all of these additional stages, along with having a role in monitoring and reviewing treatment.<sup>9</sup>

It has been suggested that for pharmacists to integrate pharmacogenetics into their practice, they will need to:

- Clinically appraise evidence and acquire relevant knowledge
- Provide relevant counselling and obtain patient consent
- Obtain, handle and test patient samples (and maintain appropriate records)
- Interpret test results and communicate these to patients, along with their wider implications, effectively
- Prescribe appropriate treatment
- Work as part of a team — solve problems, make decisions and refer when necessary
- Develop diagnostic and disease management skills
- Apply risk management

It is thought that pharmacists will also be involved in educating the public and other health professionals. Both the Department of Health<sup>10</sup> and the Royal Pharmaceutical Society<sup>11</sup> have declared support for developing the role of the pharmacist in this way.

At present, only a small number of pharmacists in highly specialised roles (eg, those providing specialist HIV services) are involved in pharmacogenetics. However, several pharmacy stakeholders believe that

## Panel 2: Definitions of terms used in the pharmacogenetic industry

The terms “pharmacogenetics” and “pharmacogenomics” are often interchanged and used collectively to refer to targeting medicines on the basis of genetic data. The data can provide information about an individual’s ability to absorb, distribute, metabolise or excrete a medicine. Alternatively, it may indicate the susceptibility of a tumour or virus to a particular medicine.

The European Agency for the Evaluation of Medicinal Products offers the following definitions:<sup>5</sup>

- Pharmacogenetics — the study of interindividual variations in DNA sequence related to drug response
- Pharmacogenomics — the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level (the term is broadly applicable to drug design, discovery and clinical development)

A pharmacogenetic test has been defined by the Nuffield Council on Bioethics as “a test to detect the presence or absence of, or change in, a particular gene or chromosome in order to predict a person’s response to a medicine”. The test can be done directly (by analysing a person’s DNA) or indirectly, by examining DNA products, such as proteins.

more pharmacists may become involved in the future as pharmacogenetics permeates a greater number of clinical areas.<sup>9</sup>

## — Preparing the profession

With the development of pharmacogenetic technology still in its infancy, the pharmacy profession should be looking to improve the education of its members. Rather than being taught how to deliver a service, pharmacists need to develop a fundamental understanding of this technology, so that they can suggest areas of clinical practice for which it could provide maximum benefit to patients.

A report commissioned by the Royal Pharmaceutical Society outlined the areas in which the profession could be involved to achieve this. These include:<sup>12</sup>

- Translating scientific research findings into working technologies and new clinical practices
- Developing new services
- Creating technical and organisational infrastructures in areas such as genetic testing
- Increasing professional knowledge and training
- Establishing new governance regimens

The factors that will influence the clinical uptake of pharmacogenetic testing are discussed in Panel 3.

## — Ethical Implications

At the heart of the debate on the ethics of pharmacogenetics is the question of whether genetic information is different to



Obtaining test samples from patients (eg, taking buccal swabs) could be one of the responsibilities of the pharmacist

other types of medical data. The Nuffield Council on Bioethics has considered the ethical implications of pharmacogenetics and has concluded that it is not different.<sup>14</sup> Therefore, it does not feel that special storage arrangements for genetic data are necessary.

However, the council did highlight that pharmacogenetic tests (similarly to some non-genetic tests) could identify or predict certain aspects of an individual's health. This

could have profound significance for treatment options and be of interest to employers and insurers. Because of the hereditary nature of genetic information, it could also be of interest to the patient's offspring and other relations. This issue could lead to patients choosing not to undergo testing because of fears surrounding the possible implications of the result.

Communicating potentially complex issues arising from pharmacogenetic testing to patients will be challenging. Presenting information about drug response appropriately and ensuring understanding will be paramount to avoid patient confusion.

## — Conclusion

There has been much hype surrounding the benefits that pharmacogenetics may deliver to patient care, much of which is unsubstantiated. However in defined clinical areas, pharmacogenetic testing may help pharmacists to improve pharmaceutical care.

Pharmacists need to have access to appropriate education and training in pharmacogenetic testing. This will allow them to keep pace with developments that may affect their practice and avoid becoming passive spectators of the expansion of knowledge in this field.

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*References on p164*

### Panel 3: Factors that will influence the uptake of pharmacogenetic testing<sup>13</sup>

**Medical need** A test that has the potential to prevent a drug from causing a life-threatening side effect will be more valuable than one that prevents a mild, self-limiting side effect. In addition, if a drug is expensive, a test that predicts its effectiveness has the potential to increase the benefit to the overall patient population by preventing the drug from being given to a patient who will not respond.

**Potential for improvement** A test will be more useful if it identifies a genetic variance that significantly, rather than marginally, affects a patient's response to a drug. For example, testing for the presence of HER2 can significantly improve the outcome of trastuzumab treatment. Understanding the relevance of pharmacogenetic testing is crucial for those who perform the tests and interpret the results.

**Clinical validity** Pharmacogenetic tests only provide predictive information, so will be most effective when they have a low probability of false positive and false negative results. Some tests that have entered clinical practice carry a risk of such results. For example, HLA B\*5701 genotyping does not guarantee whether or not a patient will be hypersensitive to abacavir. Some patients can tolerate the drug despite possessing this variant, whereas others who do not possess the variant can develop a reaction.

**Ease of use** Pharmacogenetic tests will need to be rapid and easily interpretable to be of maximum benefit.

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