**Pharmacogenetics for the prescriber**

[Munir Pirmohamed](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "!)

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**Competing interests**: Prof Pirmohamed receives research funding from various organisations including the MRC, NIHR, EU Commission and Health Education England. He has also received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); PhD studentship jointly funded by EPSRC and Astra Zeneca.

## **Abstract**

[Pharmacogenetics](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacogenetics) is the study of how [genetic factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity) affect the response to [drugs (efficacy](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-efficacy), adverse effects). Variation in genes can affect either a drug's [pharmacokinetics](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacokinetics) (how the drug is handled in the body) or its [pharmacodynamics](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacodynamics) (how it interacts with proteins in the body to produce its effects). Such variation needs to be evaluated in combination with clinical and environmental factors in order to personalize either [drug choice](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-choice) or drug dose in individual patients. There are some well-characterized examples of pharmacogenetic variation in clinical practice. As our knowledge of the human genome increases, the challenge will be to translate these findings on [genetic variation](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-variation) into clinical practice by generating evidence that shows that genotype-guided prescribing leads to better clinical outcomes than current standard practice.

## **Keywords**

Drug efficacy; drug safety; individual variability; personalized medicine; pharmacodynamics; pharmacogenetics; pharmacogenomics; pharmacokinetics; precision medicine; stratified medicine

**Key points**

•Variability in the response to drug treatment, in terms of both efficacy and safety, is the norm rather than the exception, and is related to both environmental and [genetic factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity)

•Genetic variation might influence either the choice of drug to be prescribed and/or the optimal dosage

•A number of drugs are now prescribed on the basis of a genetic test (e.g. trastuzumab for breast cancer), and this number will increase over the coming years

•Genetic variation is an important cause of increased susceptibility to adverse reactions to drugs (e.g. [abacavir](https://www.sciencedirect.com/topics/medicine-and-dentistry/abacavir), carbamazepine)

•Prescribers must be aware of (1) the drugs for which there is evidence that genetic factors determine response, (2) where they can get the relevant test carried out, and (3) how to interpret the result

## **Introduction**

Drugs are currently licensed on the basis that they show efficacy that is either equivalent or superior to a comparator, or they are superior to placebo, without adverse effects that compromise the overall benefit–risk profile of the drug. However, averaged data from populations disguise the fact that there is great interindividual variability in the response to a standard dose of most drugs. This variability is due not only to patient-related factors (non-adherence, smoking, alcohol, co-morbidities), but also, to an extent that varies from drug to drug, to [genetic factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity).[1](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "bib1) The study of these genetic factors is known as [pharmacogenetics](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacogenetics). A more recently introduced term is ‘pharmacogenomics’, which refers to the effect of the whole genome, rather than individual genes, on the response to drugs.

## **What are the sources of variability?**

Variability in [drug response](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-response) can result from [pharmacokinetic](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacokinetics) and/or [pharmacodynamic](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacodynamics) factors ([Table 1](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "tbl1)). [Drug metabolism](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-metabolism) is the most important pharmacokinetic source of variation and can be caused by [genetic variation](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-variation) in both phase I and phase II enzymes. An example of a phase I enzyme for which [genetic variability](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-variability) can lead to profound clinical consequences is [butyrylcholinesterase](https://www.sciencedirect.com/topics/medicine-and-dentistry/cholinesterase) (pseudocholinesterase): patients deficient in this enzyme suffer prolonged paralysis after the use of [suxamethonium](https://www.sciencedirect.com/topics/medicine-and-dentistry/suxamethonium), a depolarizing [neuromuscular blocking agent](https://www.sciencedirect.com/topics/medicine-and-dentistry/neuromuscular-blocking-agent) that normally has a duration of action of 10 minutes.

Variability in the expression of the [cytochrome P450](https://www.sciencedirect.com/topics/medicine-and-dentistry/cytochrome-p450) enzymes can lead to interindividual variability in metabolism of many drugs.[2](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "bib2) For example, [cytochrome P450 2D6](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyp2d6) (CYP2D6), which is responsible for the metabolism of 25% of drugs, is absent in approximately 8% of the UK population (who are called poor metabolizers). [Eliglustat](https://www.sciencedirect.com/topics/medicine-and-dentistry/eliglustat), an inhibitor of [glucosylceramide](https://www.sciencedirect.com/topics/medicine-and-dentistry/glucosylceramide) [synthetase](https://www.sciencedirect.com/topics/medicine-and-dentistry/synthetase) used in [Gaucher's disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/gauchers-disease), is metabolized by [CYP2D6](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyp2d6). Poor metabolizers should be prescribed 50% of the dose required for extensive metabolizers. Another example is that of codeine, a pro-drug metabolized to morphine by CYP2D6. Poor metabolizers do not have pain relief from codeine. Variability in phase II enzymes can also be important: for instance, mutations in the UGT1A1 gene, a member of the [glucuronyltransferase](https://www.sciencedirect.com/topics/medicine-and-dentistry/glucuronosyltransferase) family, are responsible for [Gilbert's syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/gilberts-syndrome), because of reduced [glucuronidation](https://www.sciencedirect.com/topics/medicine-and-dentistry/glucuronidation) of [bilirubin](https://www.sciencedirect.com/topics/medicine-and-dentistry/bilirubin).

Less work has been done on pharmacodynamic factors causing variation in drug response. Because drugs affect almost every protein in the body, either directly or indirectly, many genes have the potential to affect pharmacodynamic responses. A well-established example is [glucose 6-phosphate dehydrogenase](https://www.sciencedirect.com/topics/medicine-and-dentistry/glucose-6-phosphate-dehydrogenase) (G6PD) deficiency, which renders red blood cells liable to oxidative stress-induced [haemolysis](https://www.sciencedirect.com/topics/medicine-and-dentistry/hemolysis) on exposure to drugs such as [sulfonamides](https://www.sciencedirect.com/topics/medicine-and-dentistry/sulfonamide), [dapsone](https://www.sciencedirect.com/topics/medicine-and-dentistry/dapsone) and [primaquine](https://www.sciencedirect.com/topics/medicine-and-dentistry/primaquine). G6PD deficiency is now recognized to be the most common [enzyme deficiency](https://www.sciencedirect.com/topics/medicine-and-dentistry/enzyme-deficiency) worldwide and is a cause of drug withdrawal (e.g. the [antimalarial](https://www.sciencedirect.com/topics/medicine-and-dentistry/antimalarial-agent) chlorproguanil–dapsone). Adverse reactions to newer drugs have also been linked to G6PD deficiency (e.g. [rasburicase](https://www.sciencedirect.com/topics/medicine-and-dentistry/rasburicase) used to treat gout) and have caused amendments of prescribing guidance.[1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#bib1)

### **Some key examples relevant to prescribers**

The most significant genetic predictors of efficacy and adverse effects are listed in [Table 2](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "tbl2). If a patient has a genetic variant that either reduces activity (loss-of-function) or increases activity (gain-of-function), the usual prescribing decision is to avoid the implicated drug, alter the dose or continue with the implicated drug but monitor the patient more closely. A few examples are discussed in more detail below.

## **Drug efficacy**

### **Cancer therapy**

[Targeted cancer therapy](https://www.sciencedirect.com/topics/medicine-and-dentistry/molecularly-targeted-therapy) is becoming increasingly important in the management of malignant disease.[3](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "bib3) This has been made possible by our ability to detect changes in the cancer or [somatic](https://www.sciencedirect.com/topics/medicine-and-dentistry/somatics) genome. Each cancer has between 30 and 80 mutations, some of which affect the response to therapy.

The earliest example of targeted therapy was in breast cancer through the use of [anti-oestrogen](https://www.sciencedirect.com/topics/medicine-and-dentistry/antiestrogen) therapy in patients whose tumours were [oestrogen receptor](https://www.sciencedirect.com/topics/medicine-and-dentistry/estrogen-receptor) positive. More recently, the use of [trastuzumab](https://www.sciencedirect.com/topics/medicine-and-dentistry/trastuzumab) (Herceptin®) has become standard therapy for the 20% of newly diagnosed breast cancers that have an amplification of the HER2 gene or over-expression of the protein – this improves [disease-free and overall survival](https://www.sciencedirect.com/topics/medicine-and-dentistry/disease-free-survival). Recent advances have included the development of [vemurafenib](https://www.sciencedirect.com/topics/medicine-and-dentistry/vemurafenib): this targets the V600E mutation in BRAF, which promotes [cell proliferation](https://www.sciencedirect.com/topics/medicine-and-dentistry/cell-proliferation) through activation of the mitogen-activated [kinase](https://www.sciencedirect.com/topics/medicine-and-dentistry/phosphotransferase) pathway. The use of vemurafenib in the 50–60% of cases of metastatic [malignant melanoma](https://www.sciencedirect.com/topics/medicine-and-dentistry/nodular-melanoma) that carry the V600E mutation results in an overall response rate of 53% with a median overall survival of 16 months. Patients usually progress after 7 months because of secondary mutations, which has led to trials using combination therapy and more recently immune checkpoint inhibitors.

The increasing use of immune checkpoint inhibitors is adding to the complexity of identifying which patients are most likely to respond. There is emerging evidence that patients who have either a higher mutational and/or neoantigen load in the tumour are more likely to respond. A new development is tumour-agnostic drugs, which are licensed on the basis that the tumour has a molecular signature rather than its location in the body. For example, larotrectinib is indicated for patients with solid tumours who have an NTRK gene fusion.

### **Cystic fibrosis**

[Cystic fibrosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/cystic-fibrosis) is an [autosomal recessive disease](https://www.sciencedirect.com/topics/medicine-and-dentistry/autosomal-recessive-disorder) caused by many different mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. About 4% of patients have the G551D mutation, which results in a protein that is expressed at the cell membrane but is defective. This has led to the development of [ivacaftor](https://www.sciencedirect.com/topics/medicine-and-dentistry/ivacaftor), which produces marked improvements in lung function in these patients by partially restoring the lung function. The indication for the drug has subsequently been extended to a further eight mutations (which have the same functional effects as the G551D mutation) in the CFTR gene. More recent developments include the use of dual (ivacaftor in combination with tezacaftor) and triple (elxacaftor-tezacaftor-ivacaftor) therapies for the treatment of patients with the Phe508del mutation, which is the most common mutation in cystic fibrosis patients. A major issue which has caused controversy in many countries is the high cost of these therapies.

## **Drug safety**

### **Warfarin**

Individual daily dose requirements of [warfarin](https://www.sciencedirect.com/topics/medicine-and-dentistry/warfarin) vary at least 40-fold, which makes it difficult for prescribers to achieve a therapeutic but safe international normalized ratio (INR). The metabolism of warfarin via the [P450](https://www.sciencedirect.com/topics/medicine-and-dentistry/cytochrome-p450) enzyme [CYP2C9](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyp2c9) is subject to variability. This is caused by two particular variants in the CYP2C9 gene (CYP2C9\*2, [*CYP2C9\*3*](https://www.sciencedirect.com/topics/medicine-and-dentistry/cyp2c9-3)), which reduce the activity of the enzyme by up to 80%. Warfarin inhibits the enzyme [vitamin K epoxide reductase](https://www.sciencedirect.com/topics/medicine-and-dentistry/vitamin-k-epoxide-reductase) [complex 1](https://www.sciencedirect.com/topics/medicine-and-dentistry/reduced-nicotinamide-adenine-dinucleotide-dehydrogenase-ubiquinone) (VKORC1), thereby preventing the formation of activated vitamin K-dependent [clotting factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/blood-clotting-factor).

A combination of age and [body mass index](https://www.sciencedirect.com/topics/medicine-and-dentistry/body-mass-index), together with [genetic variation](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-variation) in CYP2C9 and VKORC1, accounts for at least 50% of the variation in daily dose requirements for warfarin. Dosing algorithms that take into account age, body mass index and variation in the CYP2C9 and VKORC1 genes have been developed and were tested in a [randomized clinical trial](https://www.sciencedirect.com/topics/medicine-and-dentistry/randomized-clinical-trial) (EU-PACT – European [Pharmacogenetics](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacogenetics) of Anticoagulant Therapy). This showed that the genotype-guided prescribing of warfarin improved the time in the therapeutic INR range by 7% compared with standard care.[4](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "bib4)

### **Immune-mediated adverse drug reactions**

These reactions are characterized by [rashes](https://www.sciencedirect.com/topics/medicine-and-dentistry/exanthem) and occasionally by the involvement of other organs such as the liver, kidney, lungs, bone marrow, heart and colon (either in combination with the rash or in isolation). Immune response to antigens, including those derived from drugs, is partly under the control of the [human leucocyte antigen](https://www.sciencedirect.com/topics/medicine-and-dentistry/human-leukocyte-antigen) (HLA) genes on [chromosome 6](https://www.sciencedirect.com/topics/medicine-and-dentistry/chromosome-6), which is the most polymorphic region of the human genome. Variation in the HLA genes is an important determinant of susceptibility to these immune-mediated adverse reactions ([Figure 1](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "fig1)). With the [anti-HIV](https://www.sciencedirect.com/topics/medicine-and-dentistry/anti-human-immunodeficiency-virus) drug [abacavir](https://www.sciencedirect.com/topics/medicine-and-dentistry/abacavir), hypersensitivity reactions characterized by rash, fever and gastrointestinal and respiratory manifestations, normally seen in 5% of patients, can be prevented by [genotyping](https://www.sciencedirect.com/topics/medicine-and-dentistry/genotype) for HLA-B\*57:01 before prescription and avoiding abacavir in those patients who carry the allele. This is also a cost-effective approach, which has now been mandated through changes in the summary of product characteristics and guidelines from [HIV](https://www.sciencedirect.com/topics/medicine-and-dentistry/human-immunodeficiency-virus) societies.

A strong [genetic association](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-association) has been shown in Han Chinese patients between HLA-B\*15:02 and [Stevens–Johnson syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/stevens-johnson-syndrome) caused by the [antiepileptic drug](https://www.sciencedirect.com/topics/medicine-and-dentistry/anticonvulsant) [carbamazepine](https://www.sciencedirect.com/topics/medicine-and-dentistry/carbamazepine). In white and Japanese patients, a different HLA allele, HLA-A\*31:01, acts as the [predisposing factor](https://www.sciencedirect.com/topics/medicine-and-dentistry/disease-predisposition) for carbamazepine-induced hypersensitivity reactions (including [maculopapular exanthema](https://www.sciencedirect.com/topics/medicine-and-dentistry/maculopapular-rash), [hypersensitivity syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/dress-syndrome) and Stevens–Johnson syndrome).[5](https://www.sciencedirect.com/science/article/pii/S1357303916300500" \l "bib5) Other genetic associations between the HLA genes and drug-induced toxicities affecting the skin and liver are shown in [Figure 1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#fig1).

## **Future perspectives**

At least 0.1% of the human genome is variable, and this accounts for the interindividual differences seen in the human population, including the beneficial and [adverse effects of drugs](https://www.sciencedirect.com/topics/medicine-and-dentistry/adverse-effects-of-drug). Many different variants that alter the response to a drug have been identified ([Table 2](https://www.sciencedirect.com/science/article/pii/S1357303916300500#tbl2)). Our ability to interrogate the human genome is improving all the time, and this will undoubtedly lead to the identification of many other [genetic variations](https://www.sciencedirect.com/topics/medicine-and-dentistry/genetic-variation) affecting the response to drugs. However, it is also important to note that many of these variants will act not in isolation but in combination with environmental factors. Thus, a holistic approach that takes into account both environmental and [host factors](https://www.sciencedirect.com/topics/medicine-and-dentistry/host-factor) will be needed to ensure the patient is given the right drug, at the right dosage, at the right time to maximize efficacy and minimize harm.[1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#bib1)

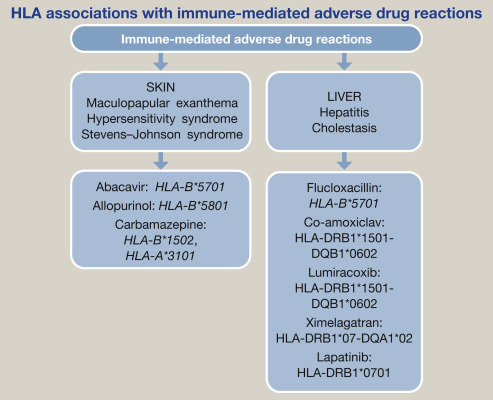
[**Pharmacokinetic**](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacokinetics) **and** [**pharmacodynamic**](https://www.sciencedirect.com/topics/medicine-and-dentistry/pharmacodynamics) **factors determining variability in** [**drug response**](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-response)

|  |
| --- |
| **Pharmacokinetic**  •Absorption  •Distribution  •Metabolism  •Excretion |
| **Pharmacodynamic**  •Enzymes  •Receptors  •Ion channels  •Transporters |

**Table 1**

| **The clinically most significant genetic predictors of** [**drug response**](https://www.sciencedirect.com/topics/medicine-and-dentistry/drug-response) | | |
| --- | --- | --- |
| **Organ or system involved** | **Associated gene/allele** | **Drug/drug response phenotype** |
| **Blood** | | |
| Red blood cells | *G6PD* | Primaquine-induced haemolysis |
| Neutrophils | *TPMT, NUDT15* | Azathioprine/6-mercaptopurine-induced neutropenia |
|  | *UGT1A1\*28* | Irinotecan-induced neutropenia |
| Platelets | *CYP2C19\*2* | Stent thrombosis with clopidogrel |
| Coagulation | *CYP2C9\*2*, *\*3*, *VKORC1* | Warfarin dose requirement |
| **Brain and peripheral nervous system** | | |
| CNS depression | *CYP2D6\*N* | Codeine-related sedation and respiratory depression |
| Anaesthesia | Butyrylcholinesterase | Prolonged apnoea with suxamethonium |
| Peripheral nerves | *NAT2* | Isoniazid-induced peripheral neuropathy |
| **Drug hypersensitivity** |  | See [Figure 1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#fig1) |
| **Drug-induced liver injury** |  | See [Figure 1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#fig1) |
| **Infection** | | |
| HIV-1 infection | *CCR5* | Maraviroc efficacy |
| Hepatitis C | *IL28B* | α-Interferon efficacy |
| **Malignancy** | | |
| Breast cancer | *CYP2D6* | Response to tamoxifen |
| Chronic myeloid leukaemia | *BCR-ABL* | Imatinib and other tyrosine kinase inhibitors |
| Colon cancer | *KRAS* | Cetuximab efficacy |
| Gastrointestinal stromal tumours | *KIT, c-kit* | Imatinib efficacy |
| Lung cancer | *EGFR* | Gefitinib efficacy |
|  | *EML4-ALK* | Crizotinib efficacy |
| Malignant melanoma | *BRAF V600E* | Vemurafenib efficacy |
| **Muscle** | | |
| General anaesthetics | Ryanodine receptor | Malignant hyperthermia with general anaesthetics |
| Statins | *SLCO1B1* | Myopathy/rhabdomyolysis with simvastatin |
| CNS, [central nervous system](https://www.sciencedirect.com/topics/medicine-and-dentistry/central-nervous-system); [HIV](https://www.sciencedirect.com/topics/medicine-and-dentistry/human-immunodeficiency-virus), [human immunodeficiency virus](https://www.sciencedirect.com/topics/medicine-and-dentistry/human-immunodeficiency-virus).  Adapted from Ref. [1](https://www.sciencedirect.com/science/article/pii/S1357303916300500#bib1). | | |

**Table 2**



**Figure 1**

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