# Pharmacogenomics

## Practice and challenges

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### Background

Generating revenue of over $1 billion annually to owner companies, blockbuster drugs have been a prominent feature of drug development over recent decades. However, a large number of patients have an inadequate therapeutic response to the 'one size fits all' blockbuster drugs. It is difficult to predict which patient subgroups will respond well to a drug and which will have significant adverse reactions.

### Objective

This article outlines the potential role of pharmacogenomics in drug development and personalised medicine in order to examine possible treatment strategies targeted to patients according to their genetic profile.

### Discussion

Drug development based on pharmacogenomics has the potential to result in medications that have predictable responses in ethnic or racial patient subpopulations and can be targeted to accommodate individual genetic variation. The key challenges for the successful implementation of this concept include finding suitable biomarkers, bringing down the cost of laboratory investigations, and making drug development processes based on pharmacogenomics economically viable for pharmaceutical companies.


**Keywords:** pharmacogenetics; individualised medicine; forecasting

'Blockbuster drugs' are those which generate revenue of more than $1 billion annually to the owner company.[1] While these drugs have contributed significantly to the financial success of manufacturers, they have led to narrow product portfolios, reduced innovation, and created an abundance of 'me too' drugs that provide incremental improvements in diseases for which treatments already exist.[2] The entire process of bringing a new drug to market takes 8–12 years and can cost up to $1 billion. Despite the seemingly massive expenditure, the great majority of prescription drugs in the market today are only effective for around 40% of target patients.[3] The percentage comes down further to 20% in the field of cancer chemotherapy.[4] It is also reported that up to 40–75% of patients with asthma, 25–50% of patients with diabetes, and 20–40% of patients with depression are nonresponsive to their treatments.[3,5]

Adverse reactions can develop with any drug and can result in morbidity or mortality. In recent years the potentially blockbuster drugs, grapefloxacin and rofecoxib, have been withdrawn due to unanticipated side effects that were only revealed when the drug entered use in the general population.[6,7]

## Personalised medicine

Until recently, the reasons for widespread interindividual variability in drug efficacy, safety and selectivity remained largely unanswered. Today, along with other variables, there are genetic factors that are known to be prominent determinants of drug response (eg. age, gender, body weight, nutrition, organ function, infections and concomitant medications).[8] The idea of 'therapy with the right drug at the right dose in the right patient at the right time' has given birth to the concept of 'personalised medicine' to replace the 'one drug fits all' idea.[9] Personalised medicine is defined as, 'the management of a patient's disease or disposition by using molecular knowledge to achieve the best possible medicinal outcome for that individual'.[9] The overarching concept of personalised medicine is to tailor treatment based on information about a patient's protein, gene or metabolite profile.

## Pharmacogenomics

Pharmacogenomics takes advantage of genomic techniques such as high throughput DNA sequencing, bioinformatics and gene mapping to allow researchers to identify the genetic basis of interindividual and interracial variation in drug efficacy, metabolism, and transport.[8,10] DNA microarray is an evolving technology that can compare the activities of many genes in diseased and healthy cells, and examine patients for the presence of specific single nucleotide polymorphisms (SNPs) quickly and affordably.[11] A single microarray can screen 100 000 of the SNPs found in a human genome in a few hours.

Pharmacogenomics is the cornerstone of the concept of personalised medicine. Defined as the science that examines the inherited variations in genes that dictate drug responses, pharmacogenomics explores the ways in which these variations can be used to predict whether a patient will have a good, bad or no response to a drug.[12]

Pharmacogenomics has its roots in pharmacogenetics, which involves studying single gene mutations and their effects on drug response.

The completion of the Human Genome Project in 2003 and advances in genotyping technology, have enabled researchers to explore the entire genome and update their approach from looking at just genes to the genome as a whole.[13] The genomes of human beings throughout the world are 99% similar – the remaining 1% of the genome leads to interindividual difference in disease susceptibility and drug response. The most common DNA variation in the human genome is SNP,[14] a mutation in which a single nucleotide is substituted by another nucleotide at a given position. Medically important SNPs are those that relate to predisposition of individuals to certain diseases and differential drug responses.[14]

## Interindividual responses

### Pharmacokinetics

Genetic variations lead to differences in pharmacokinetic parameters which eventually result in interracial and interindividual variations in drug responses. With advances in the field of molecular biology, the isolation and sequencing of DNA clones of drug metabolising enzymes has become possible.[15] Testing patients before initiating drug therapy to determine ability to metabolise different classes of drugs is a key emerging area of investigation. Genetic variations in the liver enzymes that affect metabolic rate are relatively common, eg. the Cytochrome P-450 (CYP450) family and N-acetyltransferase.[15,16]

Cytochrome P-450 enzymes metabolise more than 30 classes of drugs, including antidepressants, antiepileptics and cardiovascular drugs. Patients can be separated into poor, normal and ultra rapid metabolisers of drugs by the CYP enzymes.[15] These classifications are due to variations in the associated CYP gene. When a poor metaboliser of a particular drug is given a standard dose of that drug, the drug is metabolised slowly, resulting in an increased risk of toxicity. For ultra rapid metabolisers of a drug, the regular dose may be less effective.[15] In humans, six forms of CYP450 are largely responsible for eliminating drugs: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The majority of interindividual variability depends on CYP2C9, CYP2C19 and CYP2D6 polymorphisms.[15,17]

N-acetyltransferase is another important liver enzyme which regulates acetylation of drugs in the liver. Some patients are slow acetylators while other patients are fast acetylators. Those who are slow acetylators may experience toxicity when taking normal doses of drugs (eg. procainamide, isoniazid, hydralazine and sulfonamides). Those who are fast acetylators may not respond to isoniazid or hydralazine.[16]

### Pharmacodynamics

Variations in drug response based on difference in receptor gene have become a major focus of research. Antihypertensive medications (particularly beta-blockers), hypolipidemic treatments (eg. statins) and antidiabetic medications (eg. metformin) show interindividual variations in drug response based on receptor gene differences.[18–20] Individual differences in drug response can also be observed due to differences in receptor subtype for dopamine, catecholamine and serotonin. A single substitution in serotonin (5HT) receptor may result in a large variation of response for the drug sumatriptan.[21] The most extensively researched pharmacogenomic aspect of lipid lowering therapy is with the apolipoprotein E (APOE) polymorphisms.[19] Apolipoprotein E acts as a protective agent against atherosclerosis. Three APOE isoforms: ε2, ε3 and ε4 can exist. Several studies have shown that patients with ε4 isoforms have the poorest response to the low density lipoprotein lowering effect of statins, while patients with ε2 isoforms have the strongest response.[22] Apolipoprotein E ε4 carriers have the highest risk of coronary heart disease (CHD), ε2 carriers have the lowest risk of CHD, and for ε3 carriers, the risk falls in between.[22]

## Drug development

Pharmacogenomics provides an opportunity to target subpopulations for testing, therefore eliminating unfavourable drug products earlier in the development stages and avoiding failures by excluding inappropriate patients whose genetic makeup does not suit the drug.[9,13] Transtuzumab (Herceptin) is an important example of drug development using pharmacogenomics. Transtuzumab is an anticancer monoclonal antibody that targets the HER-2 growth factor receptor on breast cancer cells. It is approved as a combination with paclitaxel for first line treatment of patients with metastatic breast cancer whose tumours specifically overexpress the HER-2 protein. It became commercially successful after the responsive subpopulation of patients was identified.

## Challenges

Moving pharmacogenomics from the laboratory to personalised medicine in the clinic is a daunting challenge. The key hurdles to introducing a personalised medicine approach to clinical practice include:

- identifying the optimal patient subpopulation for a specific therapeutic agent
- developing accurate, economical, rapid and clinically practical methods for determining the genetic makeup of specific individuals.[23]

There are also many ethical, legal and moral questions to be addressed before implementing a widespread personalised medicine model.[23,24]

- Who should have access to personal genetic information?
- How does personal genetic information remain private?
- How should personal genetic information be used?

- What would be the alternate treatment option for those who cannot afford to purchase tailored, personalised drugs?

Using pharmacogenomics as a basis for drug discovery may not be as commercially advantageous to pharmaceutical companies as the creation of blockbuster drugs because the market for personalised medicine is potentially much smaller.

Pharmacogenomic studies could also pose a challenge for drug regulatory agencies because there would be an incre ase in the number of orphan drug applications.[24] The United States Food and Drug Administration (FDA) defines an orphan drug as one which is used for treatment of diseases that occur in fewer than 200 000 patients. It is conceivable that more companies would demand that their products be given special incentives and benefits under orphan drug applications.[24]

## Future medical practice

The inclusion of pharmacogenetic data such as CYP polymorphisms has already started to appear on drug package inserts. The package insert for warfarin contains information for clinicians regarding drug dosing and how people's responses may vary depending on genetic polymorphism.[25] However, integration of pharmacogenomic testing into future medical practice would depend largely on physicians and patients accepting the tests. In a reported study from Germany, 60% of patients and 52% of general practitioners appreciated the importance of pharmacogenetic tests in diseases such as asthma.[26] Major concerns expressed by GPs about implementing pharmacogenomics in routine medical practice are:

- undue pressure on patients to undergo testing
- negative psychological consequences of testing
- the possibility of discrimination based on test results
- potential violation of privacy.[26]

Those in favour of personalised medicine see a future in which each individual, on the day of their birth, is provided with full genomic sequence to place into a personal medical record. Patients would carry their entire genomic sequence in computer microchips and doctors would look at this before prescribing medicine. The information from the patient's personal genome would allow physicians to develop a more proactive and personalised healthcare approach based on the patient's susceptibility to different diseases and potential response to treatment.

## Conclusion

Personalised medicine is poised to transform healthcare over the next several decades. The natural variations (DNA polymorphisms) found in human genes play a role in disease risk and new diagnostic and prognostic tools will increase our ability to predict the likely outcome of drug therapy.

Personalised medicine still has a long way to go, but in many ways it can be regarded as the 21st century's answer for the rational use of drugs – the right drug at the right dose in the right patient at the right time.

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