Why you should read this article:
- To understand the principles of pharmacogenomic testing
- To be aware of how pharmacogenomic testing can inform prescribing decisions
- To familiarise yourself with the role of nurses in pharmacogenomic testing

Understanding pharmacogenomic testing and its role in medicine prescribing

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Abstract

When making prescribing decisions, it is important for healthcare professionals to remember that individual patients may respond differently to medicines. For example, some patients may experience a therapeutic benefit while others may experience an adverse drug reaction. The aim of personalised medicine is to tailor treatment based not only on a patient's clinical factors, but also on their genetic profile. Pharmacogenomics is a branch of personalised medicine that is concerned with how differences in people's genomes affect their response to medicines. Pharmacogenomic testing, which recently has become less expensive and more available, can inform nurses' prescribing decisions and improve patient outcomes. This article introduces personalised medicine and pharmacogenomics, describes how pharmacogenomic testing can optimise medicine prescribing, and explains the role of nurses in the process.

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Keywords

adverse reactions, clinical, ethical issues, genetics, genetic testing, genomics, medicines, nurse prescribing, pharmacists, pharmacology, prescribing, professional

Key points

- ***Healthcare professionals are required to weigh the potential benefits of a medicine against its potential side effects and only prescribe when the expected benefits are greater than the risk of harm***
- ***Pharmacogenomics is concerned with how differences in people's genetic material affect the way they process and respond to medicines***
- ***Pharmacogenomic testing can improve the safety and efficiency of prescribing***
- ***In the UK, nurse prescribers may use pharmacogenomic testing to guide their choice of medicine and dose***

In healthcare, patients often do not respond to prescribed medicines as expected. Some experience the therapeutic benefit of a medicine while others experience side effects, which can be so severe that they require hospitalisation. One of the challenges of prescribing is that each patient is unique, yet historically medicines have been prescribed as if there were no variation between patients. Personalised medicine challenges this practice because it seeks to tailor treatment to a patient's individual needs, which can be partly determined based on information contained in their genes (Singh 2020).

In the UK, the government recently announced the roll-out of the NHS Genomic Medicine Service (Health Education England 2019), which means that personalised medicine may eventually become the new standard of care in the NHS. This article introduces personalised medicine and pharmacogenomics, describes how pharmacogenomic testing can optimise medicine prescribing, and explains the roles and responsibilities of nurses in supporting patients to make informed decisions regarding genetic testing and treatment.

Challenges of prescribing

When prescribing, healthcare professionals are required to weigh the potential benefits of a medicine against its potential side effects and only prescribe when the expected benefits are greater than the risk of harm (Joint Formulary Committee 2019). Prescribing medicines that are safe and efficacious is challenging and a 'trial and error' approach is often used; for example, approximately 15% of patients with epilepsy spend between two and five years trying different anti-epileptic medicines before finding one that provides therapeutic benefit (Delen et al 2019).

Adverse drug reactions represent a significant burden for individuals and healthcare systems, contributing to 5-7% of hospital admissions (Pirmohamed et al 2004), and approximately 3% of deaths in the general population (Wester et al 2008).

Traditionally, adverse drug reactions have been classified into two types, type A and type B (Rawlins 1981). Both types of adverse drug reaction have genetic components that have various effects depending on the patient, the medicine and the disease (Alfirevic and Pirmohamed 2017). An adverse drug reaction can involve one or several genes, or an interaction between a gene and the environment. For example, a haemorrhage experienced following administration of warfarin sodium constitutes a type A adverse drug reaction, which is influenced by variations in three separate genes, including those that affect the medicine's metabolism in the body and factors such as the patient's age (US National Library of Medicine 2020).

Type A adverse drug reactions

Type A adverse drug reactions are dose-dependent and can be predicted by considering the clinical factors that affect the pharmacokinetics of a medicine – that is, its absorption, metabolism, distribution and excretion (Osanlou et al 2018). The pharmacological effect of a medicine depends on its concentration at the target site of action in the body, which is related to dose and concentration in the blood. If the concentration is too low, there may be no pharmacological effect; if the concentration is too high, a type A adverse drug reaction may develop (Ferner and Aronson 2019).

To reduce the risk of type A adverse drug reactions, prescribers select a medicine and dose based on clinical factors known to affect the medicine's pharmacokinetics. For example, opioids are prescribed to older people at a lower dose than younger adults because of differences in body composition that affect the distribution of these medicines (Erdő and Krajcsi 2019).

The risk of type A adverse drug reactions can also be reduced by considering the pharmacodynamics of a medicine – that is, its action on the body. For example, prescribers would avoid prescribing two different antihypertensives with the same pharmacological effect to avoid potentiating the hypotensive effects and increasing the risk of a type A adverse drug reaction.

Type B adverse drug reactions

Unlike Type A adverse drug reactions, type B adverse drug reactions cannot be predicted from the known pharmacology of a drug. Type B adverse drug reactions have an immune component and can affect several organs including the skin, liver and heart (Rawlins 1981). Type B adverse drug reactions represent 20% of all adverse drug reactions but contribute disproportionately to the overall burden of adverse drug reactions because they are usually more severe (Karnes et al 2019). One example of a type B adverse drug reaction can be seen when anaphylaxis is caused by antibiotics such as amoxicillin (Patton and Borshoff 2018).

Personalised medicine and pharmacogenomics

The role of personalised medicine is to examine clinical and genetic factors so that the prediction, prevention and treatment of disease can be tailored to individual patients (European Commission 2020). Personalised medicine uses clinical and genetic information to inform treatment choices and characterise the underlying cause of disease for individual patients. This enables healthcare professionals to tailor treatment according to the patient's clinical factors and genetic profile. The aim is to obtain an optimal response to treatment and avoid adverse drug reactions.

Pharmacogenomics, also called pharmacogenetics, is the sector of personalised medicine that is concerned with how differences in people's genetic material (genetic material includes genomes, the sum total of an organism's deoxyribonucleic acid (DNA) affect the way they process and respond to medicines (Roden et al 2019). In theory, there is a difference between pharmacogenetics and pharmacogenomics but in practice that difference is considered arbitrary and both terms are used interchangeably. In this article, the term pharmacogenomics is used, because this is the term adopted by NHS England (Health Education England 2019).

Pharmacogenomic testing is routinely used in the NHS as part of whole-genome sequencing, which guides the management and treatment of certain cancers such as lung, breast and colon cancer (Berner et al 2019). Cancer can be considered a genetic disease characterised by an accumulation of genetic mutations that contribute to tumour growth. Testing the genome of cancer cells can provide insights that support the diagnosis and management of the disease (Chan et al 2019).

Outside the domain of cancer, genetic testing of inherited genomes can assist in explaining the variability in the pharmacokinetic and pharmacodynamic action of medicines that is observed in the general population (Roden et al 2019). It is estimated that up to 95% of the population carry at least one variant of a gene that can disrupt their response to a medicine by interfering with its pharmacokinetics or pharmacodynamics (Bank et al 2019).

Inherited response to medicines

If the genome can be described as the 'instruction manual' for building proteins, which are the basic units of life, then the 'text' in that instruction manual is the DNA (Dor and Cedar 2018). DNA comprises sequences of nucleotide bases split into sections called genes. Genes encode the information required to create the proteins needed in biological processes. Alleles are variants of the same gene with small differences in their DNA base sequence, which ultimately leads to variations in the types of proteins produced. Some genes are polymorphic, which means that there are multiple alleles of those genes (Orrico 2019).

Pharmacogenes are genes that encode the information required to create the proteins involved in the action, toxicity or metabolism of medicines (Orrico 2019). Pharmacogenes with clinical significance are those in which genetic polymorphisms produce variations of proteins that affect the pharmacokinetics or pharmacodynamics of medicines, potentially leading to severe side effects or a lack of therapeutic effect at the usual doses. For example, carrying a gene polymorphism for one of the liver enzymes belonging to the cytochrome P450 (CYP450) superfamily can have significant effects, because CYP450 enzymes metabolise around 90% of the medicines used in humans (Isvoran et al 2017). Differences in the genes coding for CYP450 enzymes alter the activity of these enzymes, leading to higher or lower plasma concentrations of the medicines they metabolise (Lauschke et al 2017).

Table 1 shows the different metaboliser phenotypes (the observable characteristics or traits of an organism) patients may belong to according to their gene variant coding for a CYP450 enzyme called CYP2D6. By testing patients for variants of the gene coding for CYP2D6, they can be assigned to metaboliser phenotypes. This informs how medicines metabolised by CYP2D6 are prescribed (Caudle et al 2020). In patients who are suboptimal or intermediate CYP2D6 metabolisers, lower doses of medicines would be prescribed to reduce the risk of side effects and toxicity. In patients who are ultra-rapid CYP2D6 metabolisers, doses would be increased to improve therapeutic efficacy.

Table 1. Observed characteristics of different CYP2D6 metaboliser phenotypes

Suboptimal metaboliser	Intermediate metaboliser	Normal metaboliser	Ultra-rapid metaboliser
» Little or no enzymatic activity » Potentially toxic levels of medicines in plasma » Increased risk of side effects	» Reduced enzymatic activity » Potentially high levels of medicines in plasma » Increased risk of side effects	» Normal enzymatic activity » Normal levels of medicines in plasma » Normal response to medicines	» Increased enzymatic activity » Low levels of medicines in plasma » Reduced therapeutic efficacy of medicines

(Adapted from Caudle et al 2017, Caudle et al 2020)

CYP450 enzyme metaboliser status is also important in the prescribing of pro-drugs. Pro-drugs are medicines that have to be metabolised to be biologically active. One example of a pro-drug is codeine phosphate. Codeine is converted by CYP2D6 into its active metabolite morphine, which then provides analgesia (Joint Formulary Committee 2019). Patients who are suboptimal CYP2D6 metabolisers derive no therapeutic benefit from codeine because they are unable to metabolise it into its active form. Patients who are ultra-rapid CYP2D6 metabolisers convert codeine into morphine more rapidly and more completely than the rest of the population; therefore, if they are prescribed the usual doses of codeine, they may develop symptoms associated with morphine toxicity such as drowsiness, confusion and breathing difficulties (Yamamoto et al 2019).

Around 8% of patients of European descent carry gene variants that confer a suboptimal CYP2D6 metaboliser status (Gaedigk et al 2017). As well as metabolising analgesics such as codeine and tramadol hydrochloride, CYP2D6 also metabolises many antidepressants and antipsychotics (Dutch Pharmacogenetics Working Group (DPWG) 2020).

Pharmacogenomic prescribing

Genetic testing of patients for CYP2D6 is routinely undertaken in some medical centres in the US and the Netherlands to ensure the appropriate doses of medicines are prescribed (Dunnenberger et al 2015, Leiden University Medical Centre 2020). The number of studies evaluating the cost-effectiveness of pre-emptively testing common pharmacogenes is still limited but growing, with a number of pharmacogenomic implementation sites separately conducting clinical trials evaluating the benefits of pre-emptively testing patients for multiple pharmacogenes simultaneously (Krebs and Milani 2019).

Two organisations have been set up to publish evidence-based pharmacogenomic-prescribing recommendations, the Clinical Pharmacogenetics Implementation Consortium (CPIC) in the US and the DPWG in the Netherlands (Bank et al 2018). Both have independently published guidelines that cover many commonly prescribed medicines (CPIC 2020, DPWG 2020). Table 2 provides examples of common medicines for which pharmacogenomic prescribing recommendations are available.

Table 2. Commonly prescribed medicines for which pharmacogenomic prescribing recommendations are available

Therapeutic area	Therapeutic group and example medicines
Cardiovascular	» Anticoagulants and/or antiplatelets such as warfarin sodium » Anti-arrhythmics such as metoprolol tartrate » Statins such as simvastatin
Gastrointestinal	» Anti-emetics such as ondansetron » Immunomodulatory medicines such as azathioprine » Proton pump inhibitors such as omeprazole
Mental health	» Antidepressants such as sertraline and citalopram » Antipsychotics such as zuclopenthixol
Pain	» Opioids such as codeine phosphate
Other	» Anti-epileptics such as carbamazepine » Cancer medicines such as tamoxifen

(Adapted from PharmGKB 2020)

Benefits and limitations of pharmacogenomic testing

Advances in technology mean that pharmacogenomic testing has become less expensive and its availability is increasing worldwide (Abou Diwan et al 2019). Commercial pharmacogenomic testing, covering a limited selection of the most common genetic variants, typically costs approximately £100 for one individual in the UK. Conducting a pharmacogenomic test is relatively simple and non-invasive. Most laboratories test DNA samples collected from saliva or buccal (cheek) swabs (Ang et al 2018). Depending on the number and location of genes tested, results can take between one hour for point-of-care testing covering a limited range of gene-medicine interactions, and 1-2 weeks for reports covering a wider range of gene-medicine interactions (Moyer and Caraballo 2017).

Pharmacogenomic testing improves the safety and efficiency of prescribing. One of its most effective applications in clinical practice has prevented immune-mediated adverse drug reactions to HIV medicines and anti-epileptic medicines (Ferrell and McLeod 2008, Mallal et al 2008). Abacavir is an antiretroviral drug used in the management of patients with HIV (Joint Formulary Committee 2019). In the absence of pharmacogenomic testing, 5-8% of patients who take abacavir experience a hypersensitivity reaction during the first six weeks of treatment (Ma et al 2010). Pharmacogenomic testing identifies patients who carry a genetic variant that predisposes them to a hypersensitivity reaction to abacavir. Prescribers can use the test results to decide whether abacavir is likely to be safe for the patient or not. Systematic reviews have found that pharmacogenomic testing for preventing adverse drug reactions is effective and cost-effective for several gene-medicine pairs (Plumpton et al 2016, Zhu et al 2020).

Pharmacogenomic testing can guide dosing. For example, the way in which patients respond to warfarin sodium is influenced by several genes (Johnson et al 2017). Knowledge of these gene variants can predict patients' sensitivity to the drug and guide prescribers in adjusting the dose accordingly, thereby reducing the risk of adverse drug reactions. Pharmacogenomic testing can also guide prescribers in the selection and dosing of medicines to achieve therapeutic benefit more quickly. This is especially important in mental health, where patients often need to take medicines for at least 6-8 weeks before benefits are observed because of complex cognitive neuropsychological pathways (Harmer et al 2009, Joint Formulary Committee 2019). Selecting an inappropriate antidepressant can lead to several months of treatment without therapeutic benefits, during which symptoms can persist or deteriorate. Pharmacogenomic testing can support the identification of patients who metabolise certain antidepressants too rapidly and completely, which means the levels of antidepressants in their bodies are too low to have an effect. A recent systematic review and meta-analysis demonstrated that people with major depressive disorder receiving pharmacogenomic-guided prescriptions were 1.71 times more likely to achieve symptom remission than patients who received treatment as usual (Bousman et al 2019).

Other potential benefits of pharmacogenomic testing include:

» Supporting deprescribing (discontinuation of medicines).
» Improving patients' adherence to medicines.
» Promoting shared decision-making between prescriber and patient.

However, further research is needed in these areas (Charland et al 2014, Saldivar et al 2016, Arandjelovic et al 2017).

It is estimated that, overall, an individual's genetic profile contributes to 20-30% of the variability observed in people's response to medicines (Ingelman-Sundberg et al 2018). Consequently, a limitation of pharmacogenomic testing is that, for most gene-medicine pairs, test results cannot be read independently but must be considered alongside the clinical factors that influence a patient's response to medicines. While pharmacogenomic testing can assist in reducing the uncertainty associated with prescribing, it will never eliminate this uncertainty.

Role of nurses

The growing use of personalised medicine and pharmacogenomics has important repercussions for nursing practice across various specialties and settings.

In the UK, one study explored the implementation of point-of-care pharmacogenomic testing for warfarin prescribing in three outpatient clinics run by anticoagulant nurses (Jorgensen et al 2019). As part of the study, nurses were given questionnaires exploring their experiences of delivering the service. They responded positively to questions about their understanding of sample collection, dose calculation and giving information about pharmacogenomic testing. However, respondents were less positive about the timing of testing and how it fitted with the running of the clinic. The pharmacogenomic test used in the study required an initial discussion with the patient, a 45-minute wait for results, and a further consultation to determine dosing. Jorgensen et al (2019) commented that a potential solution could be to separate the testing from the clinic consultation so that the results would be available at the first consultation. This

could, however, mean that patients would have to make two visits to the clinic, which could reduce acceptability. The study emphasised the challenges of introducing innovations that disrupt existing clinical pathways and how important it is to engage stakeholders in the design and delivery of new services.

In the US, where pharmacogenomic testing is more common, nurse practitioners are able to order tests for their patients (Harmer et al 2009, White et al 2019, Cincinnati Children's 2020), and have a role in educating patients and informing them of their test results (White et al 2019).

Pharmacogenomic testing can be seen as a complementary tool for medicine prescribing. In the UK, nurse prescribers may use it to guide their choice of medicine and dose. According to the authors' experience, examples of scenarios where nurse prescribers could use pharmacogenomic testing include:

» To support deprescribing and optimisation of medicines in cases of polypharmacy in primary care.
» To formulate postoperative pain management plans in pre-ambulatory clinics.
» To prescribe medicines for patients with depression and anxiety in general practice.

Nurses in all specialties and settings have a role in explaining to patients what pharmacogenomic testing is and why it may be relevant to their care, supporting them to make informed decisions regarding testing and treatment. Studies that have explored patient perceptions report that patients who undergo pharmacogenomic testing generally perceive it as being of value (Haga et al 2016), but also that challenges in obtaining patients' consent for testing remain. Reported patient concerns include potential lack of confidentiality and discriminatory consequences such as being denied treatment (Haddy et al 2010, Lee et al 2018).

It will be important for nurses to explain to patients that pharmacogenomic testing concerns the manner in which patients respond to medicines, not to their susceptibility to disease or elements concerning their descent (some patients may perceive that, because a pharmacogenomic test is a DNA test, it can reveal information about genealogy). Pharmacogenomic test results should be subject to the same confidentiality and privacy rules that govern other test results in the NHS and worldwide. They should be used alongside the patient's medical history and clinical factors to guide the choice and dose of medicine, with the aim of anticipating the response to treatment (Haga 2019).

Alongside other healthcare professionals, nurses will require training on pharmacogenomic testing (Hippman and Nislow 2019). Health Education England offers free online genomics courses for those who work for the NHS and UK universities (www.genomicseducation.hee.nhs.uk). In the US, PharmGKB hosts an open access online repository of searchable pharmacogenomic information, which is funded by the National Institutes of Health and run by Stanford University (PharmGKB 2020).

Conclusion

Pharmacogenomic testing has the potential to transform the way medicines are prescribed in the NHS. It can improve the safety and efficiency of prescribing and guide the selection and dosing of many common medicines, thereby potentially improving patient outcomes and reducing the use of NHS resources.

Pharmacogenomic testing could become routine practice in the NHS within the next five years, although this is likely to be reactive; for example, screening patients who react unfavourably to medicines such as antidepressants and statins. In primary care, nurses may begin to use pharmacogenomic testing to guide prescribing in patients who have not tolerated an initially prescribed antidepressant. In the outpatient setting, nurses could use pharmacogenomic testing to support prescribing for patients seen in cardiology and pain clinics.

Nurses can have an important role in explaining pharmacogenomic testing to patients, informing them of their test results and clarifying how the test results can be used to tailor treatment.

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