

This fact sheet describes the field of pharmacogenomics (pharmacogenetics), where a person's genetic make-up is used to determine a response or possible side-effects from the use of particular drugs/medication.

In summary

- **The terms pharmacogenomics and pharmacogenetics are often used interchangeably. In this fact sheet we will refer to both fields as pharmacogenomics**
- **Pharmacogenomics looks at how a number of genetic variants in a person's DNA can influence their response to drugs or medications**
- **There are a number of benefits of pharmacogenomics; however there is still debate about its everyday use in healthcare**
- **To date there are no approved pharmacogenomics tests in Australia.**

Findings from the Human Genome Project made it clear that 99.9% of the information in the estimated 20,000 human genes is identical from one person to the next. The small differences in the remaining 0.1% of genes present in human cells are unique to each individual.

Usually these differences do not cause any problem with how our body grows, develops or works.

These variations however may influence an individual's susceptibility to certain health problems or determine how an individual's body reacts to different treatments, in particular, how different medicines are metabolised.

PHARMACOGENOMICS

The term **pharmacogenomics** comes from the combination of two words: **pharmacology** and **genomics**.

- **Pharmacology** is the study of how drugs work in the body and **genetics** is the study of how characteristics that result from the action of a single gene or of several genes acting together are inherited and how they work in the cells of the body.
- Therefore, **pharmacogenomics** is the study of genetic factors that influence how a drug works.

Factors that influence how an individual responds to medication include their external and internal environments and overall health, as well as their genetic make-up.

The goal of pharmacogenomics is to understand the role that an individual's genetic make-up plays in how well a medicine works, as well as what side effects are likely to occur in the individual's body. Understanding this can help tailor drugs for a particular individual (personalised medicine) or group of people.

Some potential benefits of pharmacogenomics:

- **More powerful medicines:** Drugs may be developed targeting specific health problems that will maximise therapeutic effects but decrease damage to nearby healthy cells.
- **Safer drugs the first time:** Doctors could have an idea which drug to use based on a genetic profile versus trial and error, decreasing the likelihood of adverse reactions.
- **More accurate methods of determining dosages:** Instead of dosages being based on body weight and age, it would be based on an individual's genetics. This would decrease the likelihood of an overdose.
- **Better vaccines:** Vaccines made of genetic material could activate the immune system to have all the benefits of existing vaccines but with reduced risks of infections.

Some potential limitations of pharmacogenomics:

- **Many genes are likely to be involved** in how someone reacts to a drug, making targeting different drugs very complex.
- **It's time consuming and difficult** to identify the small variations in everyone's genes that may influence drug metabolism or how the condition develops.
- **The interactions with other drugs** and environmental factors will need to be determined before any conclusions are made about the genetic influence on how the drug is working.

PHARMACOGENOMICS IN PRACTICE

Drug response

Common variations in the genetic information include changes to a single letter of the four letters of the DNA code – A, T, C and G. For example, the DNA letter 'A' may be changed to a 'C' so that the message in the gene has been slightly changed.

These variations usually cause no direct problem. However, in some people it can impact on their response to a drug. Small differences in the DNA code that influence a response to certain drugs are more common in certain population groups than others.

For example, the effects of drugs called **ACE inhibitors** (angiotensin converting enzyme inhibitors) that improve symptoms and survival in cases of heart failure have been found to be greater in people of European or UK ancestry than African-Americans. Pre-treatment genetic screening of patients will eventually enable this knowledge to be applied in clinical practice.

Some drugs act by binding to specific chemicals, called receptor sites, on the surface of or within body cells. Variation in the genes that code for the receptors may mean that some people may produce receptors that do not interact well with the drug.

For example, some people have a lack of response to the drug **salbutamol**, used in the treatment of asthma, due to genetic variation in the gene that codes a receptor on the surface of smooth muscle cells lining airways of the lungs.

Drug targets

Genes may also determine how many of the receptors are produced on or within cells and genetic variation may mean that some people produce more of these sites than others.

For example, the action of the widely used antipsychotic drug **haloperidol** (Haldol) depends on its ability to bind to the dopamine (D2) receptor site. In one study, 63% of patients whose genetic make-up caused a large number of these receptor sites to be produced had a response to treatment with haloperidol whereas only 29% of patients with a smaller number of dopamine (D2) receptor sites did well on the drug.

Drug metabolism

How people absorb, break down and eliminate (metabolise) drugs in the body can also be impacted by their genes.

For example, some pain relief medications such as **codeine** require a protein produced in the liver called CYP2D6 for the drug to be used by the body, break it down and remove it. Variations in the information contained in the CYP2D6 gene determine how much of this enzyme is produced in the liver.

People who have low levels of the enzyme metabolise codeine slowly and so it will be in the body for a longer period of time and is more likely to cause side effects.

Drug development

If researchers have the ability to exclude people whose genetic make-up would make the drug being tested harmful or ineffective for them, there will be an increase in the chance that a drug will show itself useful to a particular population group. This would increase the chance that the same drug will make it into the marketplace.

Undertaking pre-genetic screening of those patients taking part in a research trial should also make the research easier, faster, and therefore less expensive.

For example, in clinical research trials for developing drugs for Alzheimer disease and other forms of dementia a gene known as *APOE* is the first gene to be identified that is associated with Alzheimer disease in later life. The *APOE* gene occurs in three forms known as E2, E3 and E4.

Having the *APOE-4* form of the gene has been shown to be associated with Alzheimer disease. *APOE-4* is also distinctly involved in drug treatment for Alzheimer disease. Individuals with Alzheimer disease who have E2 and E3 forms of the *APOE* genes respond well to the drug *Tacrine*[®], while those with *APOE-4* do not. Knowledge of the *APOE* genetic make-up of an individual with Alzheimer disease is therefore important in drug treatment.

ETHICAL ISSUES

The idea of individually targeted drug therapy is very attractive but it raises a number of ethical concerns. Firstly, a person will only benefit from pharmacogenomics if they are willing to undergo genetic testing.

This in itself can raise concerns about who should have access to that genetic information, particularly as electronic health records become more widely used.

Pharmacogenomic testing is likely to be very expensive and difficult to interpret. Genetic test results can provide information about other family members and many genetic variants are involved in a number of different conditions. Very few medical professionals have formal training in genetics to help them understand the meaning of these results for their patient, or for the family.

REGULATIONS

The Therapeutic Goods Administration (TGA) has recently adopted European Union Guidelines for pharmacogenomics to guide drug development. (<https://www.tga.gov.au/multidisciplinary-guidelines#pharmacogenomics>).

Many pharmacogenomic tests are available commercially, however none have been TGA approved. Regulation will be needed if the techniques are to be widely used including prescription guidelines, testing and usage labels. In Australia, there is no Medicare rebate for pharmacogenomics testing.