

Important points

- Pharmacogenetics is the science that underpins understanding 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 (*personalised medicine*)
- Potential benefits include:
 - Development of drugs that maximise therapeutic effects but decrease damage to nearby healthy cells
 - Prescription of drugs based on a patient's genetic profile versus trial and error decreasing the likelihood of adverse reactions
 - More accurate methods of determining dosages
 - Development of vaccines made of genetic material could activate the immune system to have all the benefits of existing vaccines but with reduced risks of infections
- Pharmacogenetics is currently being used to:
 - Determine drug responses in the treatment of cardiac, respiratory and psychiatric conditions
 - Understand how some people metabolise codeine in the liver faster than others do
 - Develop targeted drugs in areas such as psychiatry, dementia, cardiac conditions and in the treatment of breast and other cancers
- Limitations include:
 - Many genes are likely to be involved in how someone reacts to a drug, making targeting different drugs very complex
 - Identification of the small variations in everyone's genes that may influence drug metabolism or how the condition develops is very difficult and time consuming
 - 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
- Ethical issues include:
 - Personalised medicine is likely to be very expensive and may adversely impact on equity and access to drugs. This may mean that the development of drugs will be targeted to those that work well with certain population groups; any such targeting will need to be carefully implemented to avoid a perception of stigma based on ethnicity
 - The assumption that an individual's race can indicate their genetic profile for drug response is itself problematic since not all people who belong to a particular ethnic group will have the same genetic variations
- Regulation will be needed if the techniques are to be widely used including prescription guidelines, testing and usage labels

Findings from the Human Genome Project (see Genetics Fact Sheet 24) 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 the human cells are key to each individual.

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

The study of the interaction between genetics and therapeutic drugs is variously called *pharmacogenetics* or *pharmacogenomics*. The differences between the two are the initial approach of the science:

- **Pharmacogenetics** starts with an unexpected drug response result and looks for a genetic cause
- **Pharmacogenomics** on the other hand begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem

These terms are used interchangeably so the term used in this Fact Sheet is pharmacogenetics.

Pharmacogenetics

The term *pharmacogenetics* comes from the combination of two words: *pharmacology* and *genetics*.

- 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, pharmacogenetics 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 pharmacogenetics 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 in the future best suited for a particular individual (*personalised medicine*) or group.

The small differences in the genes between different population groups, or some families within a population group, that have built up over the generations can mean that they react differently to medicines.

For example, if one group of people break down a medicine very quickly or very slowly compared to others, then their genes may offer a clue as to why they respond that way. If so then it may be predicted, based on his or her genes, how someone would react to a medicine prior to giving it.

Some potential benefits of pharmacogenetics

- **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

Pharmacogenetics in practice

(a) 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 (see Genetics Fact Sheet 1). For example, the DNA letter 'A' may be changed to a 'C' so that the message from 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. This is because small differences in the DNA code groups 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.

(b) 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

- **Psychiatry**

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
- About 29% of patients with a smaller number of dopamine (D2) receptor sites did well on the drug

- **Breast cancer**

Research has shown that women with metastatic breast cancer (cancer that can spread to other organs) who over-express the protein product of the gene called HER2 have aggressive disease and a poor prognosis.

- The HER2 gene normally produces a receptor protein on the surface of the breast cells that is thought to play a role in their normal cell growth by signalling the cell to divide and multiply
- When the HER2 gene is over-expressed, extra protein receptors are produced on the cell surface. This appears to trigger the cell to grow and divide out of control, and the cell becomes cancerous (see Genetics Fact Sheet 47)

- Twenty to thirty per cent of all women with metastatic breast cancer over-express the HER2 protein
- The drug *Herceptin*[®] is an artificially developed antibody against the HER2 gene product and is called a monoclonal antibody. It is thought that *Herceptin*[®] works by binding to the receptor sites on the cell surface, thereby limiting the amount of cell division that occurs and preventing the growth of the cancer

(c) Drug metabolism

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

For example, some pain relief medications such as codeine require a protein (an enzyme) 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 than if it was metabolised quickly. Slow metabolisers of codeine are more likely to have respiratory side effects
- People who produce low levels of CYP2D6 in the liver will require smaller doses of the drugs that are eliminated by this enzyme, while fast metabolisers, people who have a lot of the enzyme, will need larger drug doses to get the same effects

(d) Drug development

Excluding from clinical trials those people whose genetic make-up would make the drug being tested harmful or ineffective for them will increase 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 clinical trial should also make the clinical trials smaller, faster, and therefore less expensive.

For example, as seen in clinical trials for developing drugs for Alzheimer disease and other forms of dementia.

- The first gene to be identified that is associated with Alzheimer disease in later life is called *APOE* (see Genetics Fact Sheet 45). 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 important in drug treatment trials

Limitations

Many genes are likely to be involved in how someone reacts to a drug. It means that targeting different drugs may be very complex.

Everyone has small variations in their genes that do not cause any problem with the way that the gene works. Since these differences may influence drug metabolism or how the condition develops, the variations would need to be identified. This process is very difficult and time consuming.

In addition other factors may influence a specific drug reaction such as interactions with other drugs and environmental factors. The influence of these factors will need to be determined before any conclusions are made about the genetic influence on how the drug is working.

Ethical issues

The idea of individually targeted drug therapy is very attractive but is likely to be very expensive, impacting on equity and access to drugs.

So the future of pharmacogenetics is most likely to be the development of drugs that work well with certain population groups. The targeting of certain groups within populations, no matter how well-intentioned, has an unfortunate history such as that seen with targeting sickle cell disease screening in the early 1970s to the American Black population without appropriate education. Any programs will need to be carefully implemented to avoid a perception of stigma based on ethnicity.

As well, the assumption that an individual's race can indicate their genetic profile for drug response is itself problematic since not all people who belong to a particular ethnic group will have the same genetic variations. A possible consequence of such genetic profiling is also the denial of treatment based on race if a pharmacogenetic test that could determine more precisely how an individual would react to a drug was not available. It may mean that people from different ethnic groups who are affected by the same condition are given different access to treatment.

Regulations

To date regulations relating specifically to pharmacogenetics or pharmacogenomics have not been established in any country. Future regulation will be needed, however, if the techniques are to be widely used. This regulation would likely involve prescription guidelines, testing and usage labels.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 24, 45, 47