

This fact sheet is about genetic testing. It describes a number of ways that a person's genetic make-up can be looked at to determine whether they have a variation which can mean they or someone else in their family is at risk of having a genetic condition

In summary

- Genetic testing involves analysis of a person's DNA or the message that the DNA code is sending to the cells of the body
- Genetic testing can be carried out on a developing baby (prenatal), during childhood or later in life
- Depending on the type of genetic condition being tested for or the type of variation, different ways of analysing the DNA will be utilised.

DNA AND GENES

Our DNA is made up of sections that code for proteins, our genes, and sections that do not code for proteins. Proteins do the work in our cells and these are very important for normal cell function and our health. Our protein coding DNA, our **genes**, do not contain much variation. Sections of our DNA that do not code for protein contain much more variation. We do not understand all the functions of these non-protein coding sections of DNA, but we know sections can be important for controlling our genes.

People generally have the same number and sequence of genes so that the same messages are sent to the body. However, there can be small variations between individuals in the information contained in specific DNA codes. Members of the same family tend to be more similar in their genes than unrelated individuals.

An example of this is eye colour. Everyone has two genes that determine eye colour, but changes in these genes can make eye colour vary, this is why some people have blue eyes, some brown, some hazel. The same gene can send different messages because of variations in the messages.

Similarly, there may be small variations in our DNA that may affect how our bodies grow and develop. Generally these variants do not have any impact on our health and are called **neutral variants** or **polymorphisms** (*poly* means many; *morphisms* means forms). Polymorphisms are quite common in the DNA code.

Some gene variations do make the gene faulty so that the message is not read correctly or is not read at all by the cell. A variation in a gene that makes it faulty is called a **mutation** or **pathogenic variant**.

WHAT IS GENETIC TESTING?

Genetic testing is the analysis of information in the DNA of an individual. There are a number of different types of genetic tests and the type of genetic test carried out will depend on the type of DNA change being tested for and also the type of genetic condition in question.

HOW IS THE TESTING DONE?

Genetic testing usually involves taking a sample of body tissue. The type depends on the particular test and may include blood, cells obtained from the lining of the cheek or the cells in the roots of an individual's hair, amniotic fluid or cells from chorionic villi sampling in pregnancy as well as a variety of body fluids and tissues.

Looking for mutations in the genetic code (direct gene testing)

If the sequence of DNA letters in a gene is not able to be read in the correct way, the protein may not be produced in the right amount, or produced in a form that will not function or is not produced at all. This can lead to health problems and may be recognised as a genetic condition.

The first step in determining the cause of a genetic condition is to locate the gene involved. The location of many of the genes in humans is now known.

The next step is to study the sequence of letters in the gene or surrounding the gene in a person's cells. It is important to determine if the sequence of letters in the gene is correct (therefore producing the right protein in the appropriate amount) or incorrect and therefore has a mutation (altering the type or amount of protein produced).

Genetic testing aims to determine whether a person has or does not have a mutation in a particular gene. This can be important information for both that person and their family for a number of reasons.

- Genetic testing can lead to the diagnosis of a genetic condition in that individual or other members of their family
- For some common conditions, the results of a genetic test may show that a person is at increased risk of developing a particular condition. This is known as **predictive testing** for conditions such as familial breast cancer
- More rarely, a genetic test can determine whether a person will develop a condition later in life, based on the presence of a mutation. This can be identified long before any symptoms are present and is called **pre-symptomatic genetic testing**. An example of a condition where this is possible is called Huntington disease.

Genomic testing (also known as whole genome sequencing, genome wide sequencing, massive parallel sequencing or next generation sequencing).

Genomic testing refers to genetic testing that looks for variations in the whole genome (all genes and the regions in between) at one time rather than looking at just one or a few genes.

For medical purposes, genomic testing is currently being used in the research setting as there is still a need for further understanding of how to analyse the enormous amount of data generated and how to manage the results.

Testing the whole genome at once means that many variants may be identified where their impact on a person's health may be:

- Unknown
- Not validated in research
- Unexpected and incidental.

At present, many health professionals and laboratories are using targeted testing (see below) until further processes are in place to analyse and best manage the complex results of full genome testing.

Targeted genetic testing

Targeted genetic testing refers to genetic testing which focuses on a group of genes and includes the following techniques:

- *Panel testing:*
 - ◊ Where a panel of related genes are tested, i.e. a panel of genes related to heart disease.
- *Exome sequencing:*
 - ◊ The exome is the coding section of DNA and makes up about 2% of an individual's entire genome. Exome sequencing uses a technique that allows multiple strands of DNA to be sequenced simultaneously. The exome is thought to contain the majority of disease-causing mutations. Analysing only 2% of the genome greatly reduces the amount of information to be filtered and the cost of the process.
- *Microarray testing:*
 - ◊ Sometimes called comparative genomic hybridisation (CGH), chromosomal microarray (CMA) testing is a detailed genetic test that can detect extra or missing segments of genetic material or DNA. A CMA test examines the amount of DNA present and looks for a variation in the number of copies of the segments. These are known as copy number variants. If the test finds a copy number variant, the laboratory will check which genes it contains and if they relate to the suspected condition. CMA testing may be suggested if a person has a pattern of development or health concerns that are suspected to be caused by extra or missing sections of DNA.

In targeted genetic testing, there is also the potential for results that are unexpected or of uncertain or unknown significance but not to the same degree as in genome wide sequencing. However expert analysis is still necessary to fully understand the implications of these results.

Genetic screening

Genetic screening involves the same processes involved in genetic testing but is undertaken for a particular condition in individuals, groups or populations where there is not a family history of the condition. The difference between genetic testing and genetic screening is the target group for the testing.

WHY CONSIDER A GENETIC TEST?

a) Diagnosis

Genetic testing can be used to diagnose conditions at all stages of life, from conception to the very end of life.

b) Genetic carrier testing

People can also be **genetic carriers** of variations in genes without showing any signs or symptoms of a genetic condition. However if both parents are genetic carriers of the same mutation, there is a chance that their children may be affected by a genetic condition.

c) Genetic carrier screening

Genetic carrier screening is a direct gene test applied to a whole population or to a defined group. For example, genetic carrier screening may be available for people in the population who have no personal or family history of a condition but who have a greater than average chance of carrying a particular variation due to their ancestry.

d) Newborn screening

Genetic screening is done on all newborn babies in Australia and New Zealand by a simple blood test to detect a few rare genetic conditions. The blood sample is taken by a heel-prick before the baby leaves hospital, or for home births, on about day 4, and is sent to a special laboratory.

e) Pre-symptomatic genetic testing

Direct genetic testing is now being used to determine if a person will develop certain inherited conditions later in life. This type of genetic testing is referred to as pre-symptomatic testing where the detection of a mutation in a person with a family history of a particular condition, but who currently has no symptoms of that condition, means that that person will certainly develop the condition in later life.

Pre-symptomatic testing is available for a number of neurodegenerative diseases such as Huntington disease and some forms of bowel cancer.

f) Predictive Genetic Testing

Sometimes the detection of a specific mutation implies a person has an increased risk estimate or chance, rather than certainty, that they will develop a particular condition later in life. This type of direct gene testing is called predictive testing.

Predictive testing for some families is available for inherited conditions such as an inherited predisposition to breast cancer.

LIMITATIONS OF GENETIC TESTING

Finding that a person has a variation in a gene involved in a particular condition does not always relate to how a person is, or will be, affected by that condition. There may be modifying factors (other genes, environmental factors) that can affect the expression of the message from the gene. This may explain the variability of symptoms between affected members of the one family

Despite the recent advances in DNA analysis, identifying and understanding the meaning of variations in the DNA sequences in genes is not always easy.

- Many of the genes in which variations lead to a condition code for very large messages. Changes can occur anywhere along the length of the DNA segment making up the gene and it may take a long time to search the whole gene for a causative change.

- A single gene may have many possible variations – some make the gene faulty (mutations); others have no effect on how the gene works and others are of unknown significance. For example, there are over 1,500 mutations that have been detected to date at different places along the length of the gene involved in cystic fibrosis (CF). It is also likely that there are other mutations that have not yet been identified
- Laboratories often test for only some of the more commonly known mutations in a gene and not for the presence of those that occur much more rarely
- For some complex conditions that develop as a result of the interaction between the person's genetic make-up and other environmental or other genetic factors, for example in cancer, the testing may have to be done on a family member with the condition to identify the family-specific mutation in the gene (mutation searching) before other healthy family members can be offered predictive testing.

ETHICAL ISSUES

There are advantages and disadvantages to genetic testing. Genetic testing should only be used after all the benefits, costs and implications have been considered.

Genetic testing will usually be discussed with a specialist genetic team who can provide the most up to date information in order to ensure the genetic test is being offered and undertaken with full consent in the most informed and considered way for the individual and their family.