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## Gene therapy

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### Summary

- Gene therapy is an experimental form of treatment. It works by replacing a faulty disease-causing gene with a working version, or by introducing a new gene to cure a condition or modify its effects.
  - The aim is to eliminate genetic diseases at their source.
  - The challenge for nations experimenting with gene therapy is to come up with workable, fair and ethical guidelines for its use.
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This type of therapy is called 'therapeutic gene therapy' or 'the use of genes as medicine'. It is an experimental form of treatment that is still being developed, but it has the potential to revolutionise treatment for all kinds of genetic conditions.

Gene therapy targets the faulty genes responsible for genetic diseases. Inheriting a faulty (mutated) gene can directly cause a wide range of disorders such as cystic fibrosis and haemophilia. It can also cause susceptibility to some cancers. Gene therapy can be used to replace a faulty gene with a healthy version or to introduce a new gene that can cure a condition or modify its effects.

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### Gene therapy targets faulty genes

Genes are the blueprint for our bodies, providing information for the cells to produce proteins and enzymes to control our growth, development and health. A genetic mutation means that a gene contains a variation or 'spelling mistake' that disrupts the gene message. Sometimes, the whole or part of the gene is missing (deleted). These changes can make the gene faulty. A mutation can occur spontaneously or may be inherited.

Inheriting one or both copies of a faulty gene can cause a wide range of conditions such as haemophilia and cystic fibrosis, and can also result in increased susceptibility to some cancers. Gene therapy targets the faulty genes responsible for a genetic condition. Gene therapy can be used to replace a faulty gene copy with a working version or to introduce a new gene that can cure a condition or modify its effects.

### The gene therapy process

The basic steps of gene therapy include:

- The faulty gene that causes a specific condition must be identified.
- The location of the affected cells in the body's tissues or organs must be pinpointed.
- A working version of the gene must be available.
- The working version of the gene has to be delivered to the cell.

### A range of delivery techniques

The current problem is to find a way to successfully 'deliver' the working version of the gene. To begin with, the affected cells are taken from the person's body and the working version of the gene is either 'spliced' or injected into these cells. They are left to grow in the laboratory and then replaced into the person.

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One promising technique is to put the working gene inside a harmless virus, which has had most of its own genes removed – it has been ‘deactivated’. A virus that causes disease (such as the common cold) works by slipping into a cell, taking over its DNA and forcing it to produce more viruses. Similarly, a deactivated virus can enter the specific cell and deliver the working gene.

Other techniques involve using stem cells. These are immature cells that have the potential to develop into cells with different functions. In this technique, stem cells are manipulated in the laboratory to accept new genes that can then change their behaviour. For example, a gene might be inserted into a stem cell that could make it better able to survive chemotherapy. This would be of assistance to those patients who could benefit from further chemotherapy following stem cell transplantation.

### Some examples of gene therapy

- **Leber’s congenital amaurosis (LCA):** In February 2007, a gene therapy trial was conducted in the NIHR Biomedical Research Centre in the US with three patients (about 18 years old) with a condition called Leber’s congenital amaurosis (LCA), a rare inherited eye disease. The condition appears at birth or in the first few months of life and causes progressive deterioration and loss of vision. There are currently no effective treatments available. The trial’s purpose was firstly to find out whether gene therapy for retinal disease is safe, and secondly, to find out if it can benefit vision in young adults who already have advanced retinal disease. The cells beneath the retinas of the patients were inserted, using a very fine needle, with the modified virus in a controlled retinal detachment that resolved as the vector was absorbed. No side effects were reported and all achieved levels of vision at least equivalent to before the operation, while one patient benefited from significantly improved night vision.
- **Adenosine deaminase deficiency:** A person born with adenosine deaminase (ADA) deficiency lacks an important enzyme of their immune system. This means that infections are likely and can even be fatal. ADA deficiency was the first genetic disorder to undergo experimental gene therapy trials in 1990. It was chosen because a single, relatively uncomplicated gene causes it. The results were promising.
- **Bolstering the immune system:** Current research is focusing on the immune system, which is a collection of special cells and chemicals that fight infection. If the immune system isn’t functioning in the right way, illness can result. One theory on cancer suggests that the immune system is failing to stop the overgrowth of cells that form a tumour. If the immune system could be ‘bolstered’ with gene therapy, perhaps the body would be able to prevent the spread of cancer by itself. One day, gene therapy may also be used as a form of immunisation against particular infections, such as HIV/AIDS and malaria.
- **X-SCID:** Children affected by X-linked severe combined immune deficiency (X-SCID) have a faulty gene that means they have no working immune system, so their bodies cannot fight infections. Only boys are affected due to the pattern of inheritance of the faulty gene. Until recently, boys with X-SCID faced a lifetime living in a sterile bubble, unless they could be given a matched bone marrow transplant. With gene therapy, bone marrow from the boy is first removed to ‘harvest’ stem cells. The stem cells are then infected with a virus carrying a working copy of the X-SCID gene, before returning the cells to the boy’s body. This treatment was described in 2000. Seven out of 10 infants treated to date have restored immune function, but two of the children treated initially have developed a form of leukaemia. The leukaemia in these two patients was caused when the virus used to deliver the therapeutic gene activated a cancer-causing gene. After the first boy developed leukaemia in October 2002 and the second in January 2003, clinical trials of the gene therapy being conducted in a number of countries were halted. These have now been resumed, but only for patients with no other treatment options. Work is continuing to make the therapy as safe as possible.

### Body cells versus reproductive cells

A replaced, working gene that is inserted into the cells in the body that are affected (called the ‘somatic’ cells) would cure the individual. It would not prevent their children from inheriting the original faulty gene, however, as these are carried on the sperm and egg cells (called ‘germ’ cells).

To make sure that future generations of the person’s family were not affected by the genetic condition, their germ cells would need to undergo gene therapy too. However, a complicated range of ethical issues, as well as technical problems, means that gene therapy of germ cells is only a remote possibility.

## **The risks of gene therapy**

Some of these risks may include:

- The immune system may respond to the working gene copy that has been inserted by causing inflammation.
- The working gene might be slotted into the wrong spot.
- The working gene might produce too much of the missing enzyme or protein, causing other health problems.
- Other genes may be accidentally delivered to the cell.
- The deactivated virus might target other cells as well as the intended cells.
- The deactivated virus may be contagious.

## **More research is needed**

Gene therapy is currently an experimental discipline and much research remains to be done before this approach to the treatment of disease will realise its full potential. Between 1989 and 2010, 1698 clinical gene therapy trials were initiated or approved worldwide. So far, less than one per cent of these have shown clinical benefit.

The majority of trials are being conducted in the US and Europe, with only a modest number initiated in other countries, including Australia (1.6%). Most trials focus on treating acquired conditions such as cancer and AIDS, although an increasing number of genetic conditions are being targeted.

## **Ethics, morals and genetic engineering**

Gene therapy offers a range of complex ethical and moral dilemmas. Some people believe that gene therapy is the same thing as genetic engineering. Currently, genetic engineering is concerned with altering food crops, while gene therapy aims to eliminate disease at its source, not produce a 'better' class of human being.

The concern is that manipulating factors such as intelligence might be tried, once gene therapy becomes commonplace. 'Ordinary' characteristics, such as shortness or average IQ, might then be considered 'subnormal'.

Another concern is that gene therapy might only be available to the rich. The challenge for nations experimenting with gene therapy is to come up with workable, fair and ethical guidelines for its use.

## **Where to get help**

- Your GP (doctor)
- Victorian Clinical Genetic Services (VCGS), Royal Children's Hospital Tel.1300 118 247

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