# Medical Applications of Genetic Technologies

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Manipulating DNA has been a key component of medical research since the early 1970s, when researchers began experimenting with the genes of model organisms. The first transgenic animal was created in 1974 by introducing foreign DNA into the embryo of a mouse. Since then, research into the link between genes and disease has progressed at an exponential rate.

When the human genome project was completed in 2003, researchers had access to more information about DNA and genes than ever before. This increase in knowledge led to a boom in new genetic technologies that read, manipulate and even edit the human genome, with the aim of improving health.

Today, these technologies are being applied to diagnose rare genetic conditions, discover a person's risk of developing inherited diseases, and develop more targeted drug treatments. In the future, genetic technologies could dramatically lower the rates of inherited diseases in the human population, and revolutionise how we treat diseases like cancer.

## Reading and analysing DNA

One of the first medical applications of genetics knowledge was **genetic testing** – identifying changes (known as variants) in a person's DNA that are associated with a disease or risk. Genetic tests usually look at single genes, or parts of genes, to find variants.

In 1966, the first genetic screening program began in Australia, for the inborn error of metabolism phenylketonuria. Today, every baby born in Australia is offered screening for around 30 genetic conditions, and hundreds of additional tests for genetic conditions are available through the healthcare system. Some of these tests analyse DNA directly to look for variants. Others analyse the products of genes – such as proteins or metabolites – to determine whether a variant in DNA might be indirectly affecting pathways in the body.

**Genomic testing** is analysing is analysing large parts (or all) of a person's DNA to find variants that might be associated with a genetic condition. This technique is becoming more widespread as an alternative to single gene tests. As well as diagnosing inherited disease, genomic testing is also used to identify risks in healthy people.

Finding an underlying cause for a genetic condition can make a huge difference for patients, sometimes allowing them to find support and connect with people with similar conditions across the world. In some cases, a diagnosis can also be used to guide treatment. For people who are found to be at increased risk of developing a specific disease, genomic testing results can help their doctors develop tailored screening programs. Early detection of many conditions can increase the chance for effective treatment and reduce mortality.

Analysing the DNA of tumour cells through sequencing technologies has enabled scientists to develop **targeted cancer therapies**. These therapies kill cancer cells by blocking proteins unique to a specific type of tumour cell. One of the first such therapies, imatinib, was approved in 2001. This drug targets a protein produced from a fusion of two genes that is a hallmark of some cancers, including chronic myelogenous leukaemia.

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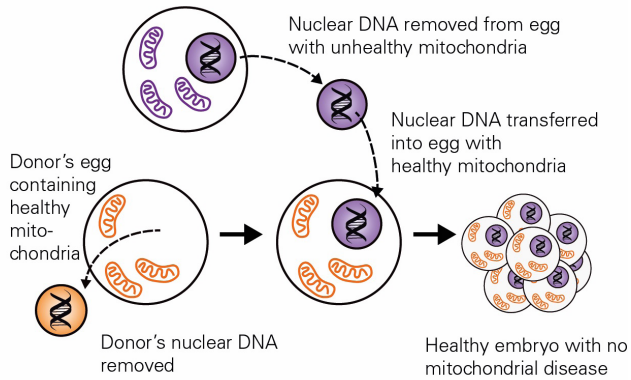
## Reproductive technologies

**Pre-implantation genetic diagnosis** (PGD) involves genetic profiling of an embryo created using in vitro fertilisation (IVF), prior to transferring it to the uterus and allowing it to develop normally. PGD is used to help couples who are at risk of passing on genetic conditions to their children. Only those embryos that do not have the genetic condition being tested for will be selected and transferred to the uterus, meaning that PGD can lower rates of many genetic conditions in the population.

The first clinical application of the technique was published in 1990, and was a study in two couples at risk of passing on X-linked conditions. The technique was initially only adopted for a small subset of diseases, but its use has now expanded to include a range of both sex-linked and autosomal conditions.

**Mitochondrial replacement therapy** is an expansion of IVF techniques that can prevent mothers passing mitochondrial diseases on to their children. Mitochondria have their own genome, and during early development it is the mother's egg cells that contribute mitochondria to the embryo.

In mitochondrial replacement therapy, a donor egg with healthy mitochondria has its nucleus removed and replaced with nucleus from the mother. IVF then produces an embryo that contains nuclear DNA from both parents and healthy mitochondrial DNA from the donor.




**Mitochondrial replacement therapy**
**Adapted from Australian Mitochondrial Disease Foundation**

In 2015, the United Kingdom became the first country to legalise mitochondrial donation. The technique is highly controversial as it involves modification of the germline, meaning that any changes made to the genome are able to be passed on through generations. There are also ethical concerns that having DNA from three parents could cause implications for the self-identity of the child.

## Genes as medicine

Introducing DNA into cells to treat or prevent disease is known as **gene therapy**. The first gene therapy trial was in 1990, showing that it was possible to use a viral vector to deliver genes into human cells. While early progress was hampered by adverse events, a number of approved gene therapies have emerged.

While most therapies are still in the research phase, in 2017 a 13-year old boy became the first person in the US to receive an FDA-approved gene therapy for an inherited disease. The therapy, known as voretigene neparvovec or Luxturna, treats a rare inherited eye disease by delivering a modified copy of the RPE65 gene to retinal cells via a viral vector.

Directly changing the DNA sequence of genes within cells could remove the need for a vector and eliminate the adverse events associated with some gene therapies. A major breakthrough was made when CRISPR-Cas9 was first harnessed for **genome editing** in human cells in 2013.

CRISPR-Cas9 is a system that evolved in bacteria as a defence against viruses. CRISPR regions are short, repeated sequences of DNA broken up with "spacer DNA" – regions of variable sequence that arise from previous exposure to viruses or plasmids. Cas9 is an enzyme that recognises the spacer regions and cuts them to remove foreign DNA from the bacterial genome.

CRISPR-Cas9 has been adapted to edit DNA in the laboratory – when injected into cells with a guide sequence, CRISPR-Cas9 can cut highly specific regions of DNA so they can be replaced with a new sequence. While the technology has not yet been used in human trials, there is a great deal of excitement around its potential applications for human health. CRISPR-Cas9 can be used to edit disease-causing genes, and if carried out at the embryonic stage, this would mean a change that reaches all cells in the body and is able to be passed on to children. Researchers successfully edited viable human embryos for the first time in 2017, however, there is considerable debate regarding the ethics of using this approach to treat genetic disease.

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## Further Reading

### Genetic and genomic testing

http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-15-genetic-and-genomic-testing

https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/about-kccg/what-is-clinical-genomics

### Preimplantation genetic diagnosis

http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-29-preimplantation-genetic-diagnosis-pgd

https://www.nature.com/scitable/topicpage/embryo-screening-and-the-ethics-of-human-60561

### Mitochondrial replacement therapy

https://www.newscientist.com/article/2107451-everything-you-wanted-to-know-about-3-parent-babies/

https://www.mito.org.au/wp-content/uploads/2016/03/Mitochondrial-Donation-Briefing-Paper.pdf

### Gene therapy

http://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-23-gene-therapy

https://www.yourgenome.org/facts/what-is-gene-therapy

https://theconversation.com/car-t-therapy-works-for-some-blood-cancers-but-can-we-make-it-work-for-brain-tumours-100125

### Gene and embryo editing

https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline

https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting

https://theconversation.com/scientists-edit-human-embryos-to-safely-remove-disease-for-the-first-time-heres-how-they-did-it-81925

https://theconversation.com/explainer-crispr-technology-brings-precise-genetic-editing-and-raises-ethical-questions-39219

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