Human Genetics and Ethics

Volume | 433

Edited by Justin Healey

ISSUES IN SOCIETY

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INTRODUCTION

Human Genetics and Ethics is Volume 433 in the 'Issues in Society' series of educational resource books. The aim of this series is to offer current, diverse information about important issues in our world, from an Australian perspective.

KEY ISSUES IN THIS TOPIC

Each cell in the human body contains about 20,000 genes. Genes carry the information that determines the traits that are passed on to you, or inherited, from your parents. Genes are the instructions for the growth and development of our bodies, however mutations in a person's genome can result in a genetic condition or disease. How do the building blocks of the human body – DNA, genes and chromosomes – interrelate and interact with the environment, and contribute to a range of serious diseases?

What are the dilemmas, risks and regulations associated with genetic testing and its related privacy and discrimination issues, the corporate patenting of people's genes, and the growing prospects of human genetic enhancement? What are the ethical implications of gene therapies and emerging biotechnology techniques like gene editing (CRISPR) in the manipulation of the human genome?

In this new era of personalised medicine are we as a species going too far, or are we on a promising path to curing many deadly diseases? Does this all amount to scientific progress, or are we playing God with our own genes?

SOURCES OF INFORMATION

Titles in the 'Issues in Society' series are individual resource books which provide an overview on a specific subject comprised of facts and opinions.

The information in this resource book is not from any single author, publication or organisation. The unique value of the 'Issues in Society' series lies in its diversity of content and perspectives.

The content comes from a wide variety of sources and includes:

- Newspaper reports and opinion pieces
- Website fact sheets
- Magazine and journal articles
- Statistics and surveys
- Government reports
- Literature from special interest groups

CRITICAL EVALUATION

As the information reproduced in this book is from a number of different sources, readers should always be aware of the origin of the text and whether or not the source is likely to be expressing a particular bias or agenda.

It is hoped that, as you read about the many aspects of the issues explored in this book, you will critically evaluate the information presented. In some cases, it is important that you decide whether you are being presented with facts or opinions. Does the writer give a biased or an unbiased report? If an opinion is being expressed, do you agree with the writer?

EXPLORING ISSUES

The 'Exploring issues' section at the back of this book features a range of ready-to-use worksheets relating to the articles and issues raised in this book. The activities and exercises in these worksheets are suitable for use by students at middle secondary school level and beyond.

FURTHER RESEARCH

This title offers a useful starting point for those who need convenient access to information about the issues involved. However, it is only a starting point. The 'Web links' section at the back of this book contains a list of useful websites which you can access for more reading on the topic.

AN INTRODUCTION TO DNA, GENES AND CHROMOSOMES

DNA contains the instructions for growth and development in humans and all living things. Our DNA is packaged into chromosomes that contain all of our genes. The Centre for Genetics Education explains

IN SUMMARY

- DNA stands for (DeoxyriboNucleic Acid) which is made up of very long chains of chemical 'letters': Adenine (A), Guanine (G), Thymine (T) and Cytosine (C).
- DNA contains the instructions for our genes.
- Genes are the instructions for making proteins. Proteins do the work within our cells and body.
- In humans, most genes are arranged on chromosomes that are found in the nucleus of cells.

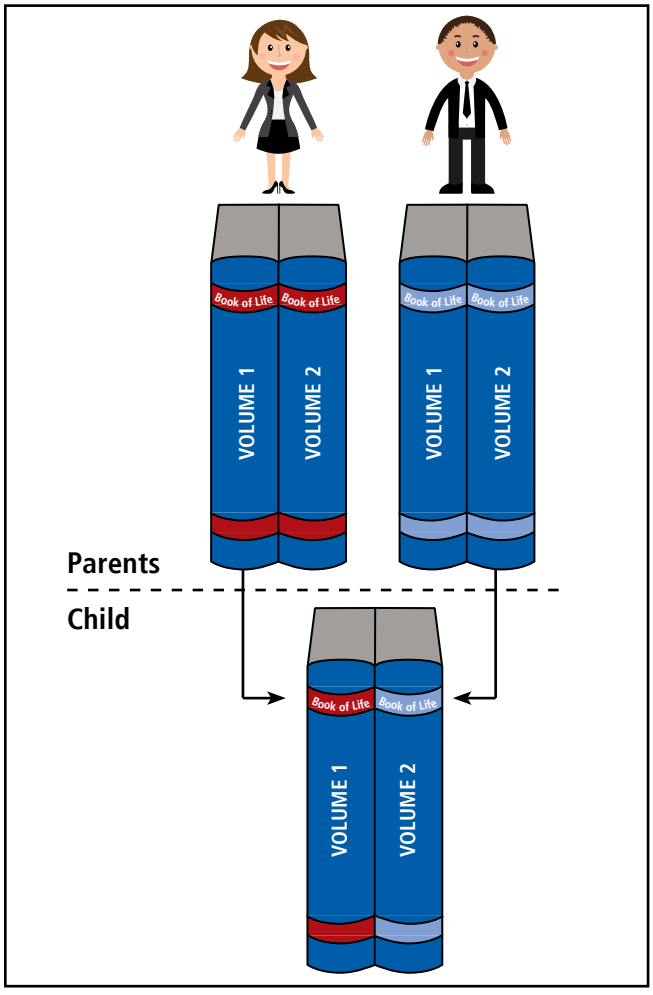
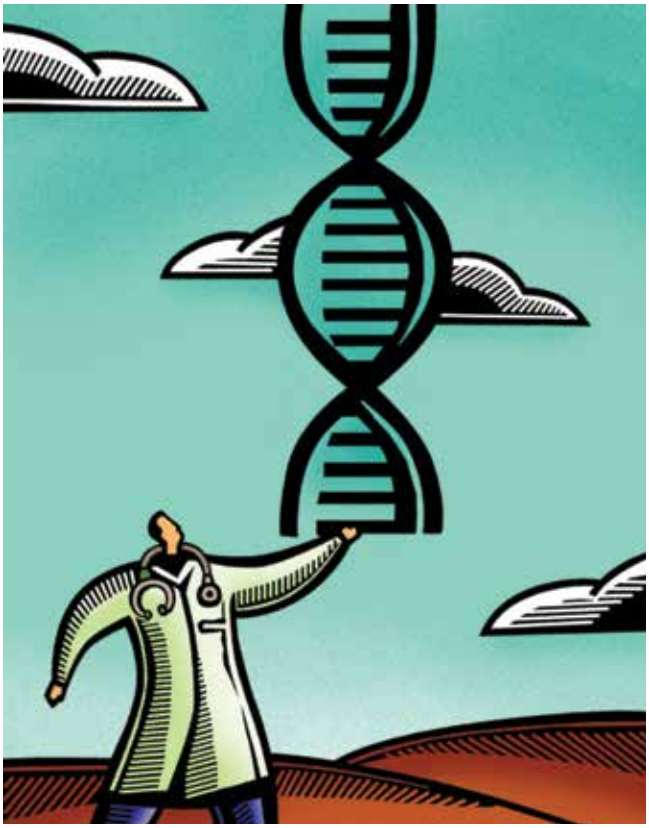


Figure 1.1: The human genome is sometimes called the 'Book of Life'.



The genetic book of life

In humans genetic information, also known as our genome, can be described as the 'Book of Life'. This book can be thought of as being made up of two volumes, each volume of the book is given to a person by one of their parents (Figure 1.1).

Reading a person's genetic book of life (Figure 1.2):

- One volume of the book is inherited from the mother and the other from the father
- Both volumes contain 23 chapters each, equivalent to the 23 pairs of chromosomes in human body cells that contain genetic information
- The 23 chapters (chromosomes) are made up of a number of recipe pages (coding DNA or genes) and

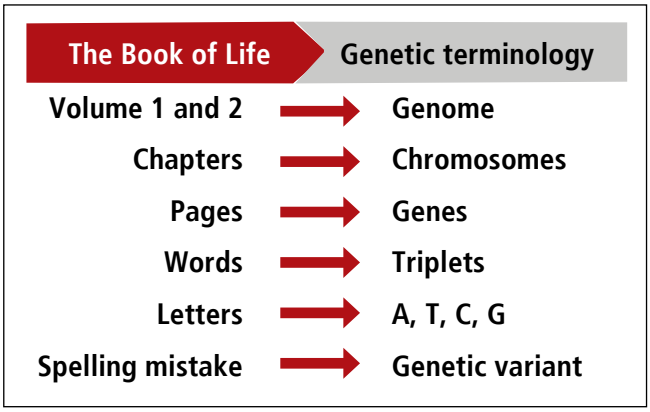


Figure 1.2: Genetic terminology and the 'Book of Life'.

in-between (non-coding) pages of DNA

- Some of the chapters contain many pages while others only have a few. Some chromosomes are large and contain many thousands of genes and non-coding DNA while others are much smaller
- Genes are sections of DNA that code for the proteins our body needs to function
- In-between (non-coding) sections of DNA have various jobs, not all of which we understand
- Careful examination of the words within genes shows that all the words are made up of three letters (triplets) such as AGT, GGT, ACT, CAA etc.
- There are four letters used in the genetic book. They are A, T, C & G.

Just as reading the words on the page of a book allows an understanding of the author's message, the body is able to read the triplets in genes to make the protein needed for our cells to work.

Our cells don't need all the instructions all the time. Pages of our genetic book can be closed and then reopened when needed. Each type of cell can have different parts of the genetic book opened or shut because different cells do different jobs in our body. Which genes are turned on or off can be influenced by our diet, chemical exposure, exercise, ageing and messages from other genes in the body.

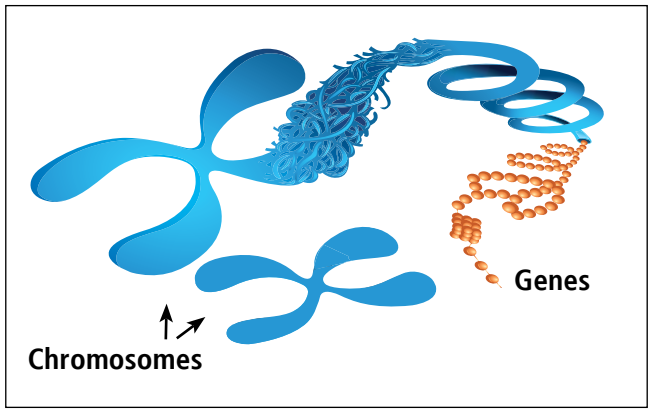


Figure 1.3: Chromosomes are like strings of genes.

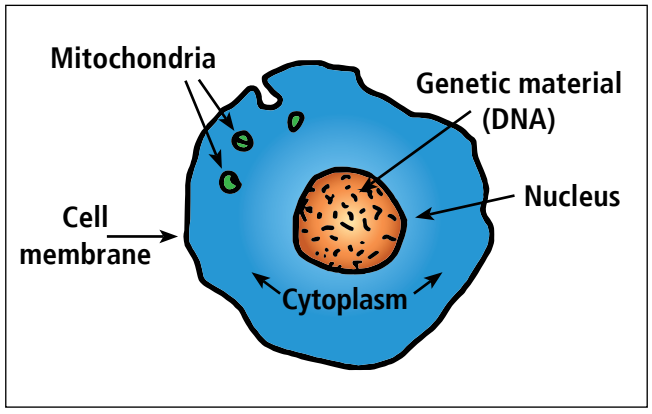


Figure 1.4: Diagram of a human cell.

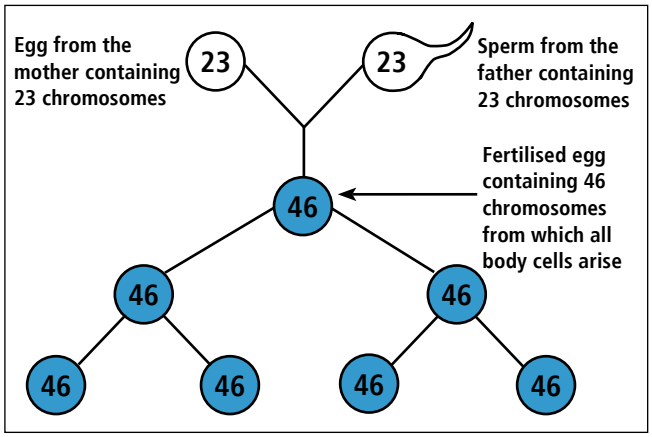


Figure 1.5: At conception the sperm and egg combine.

DNA, genes and chromosomes in the body

Our bodies are made up of millions of cells. Each cell contains a complete copy of a person's genetic book of life.

Chromosomes can be thought of as being made up of strings of genes (DNA that codes for proteins) with non-coding DNA between them. The chromosomes, including the genes, are made up of a chemical substance called DNA (DeoxyriboNucleicAcid).

The chromosomes are very long strands of DNA, coiled up like a ball of string as shown in Figure 1.3.

Chromosomes are found in the nucleus of all body cells except for red blood cells which have no nucleus and therefore do not contain chromosomes.

Another place in the cell where DNA is found is in very small compartments called mitochondria (the energy centres of the cell) that are found scattered outside the nucleus (Figure 1.4). The DNA in mitochondria is much smaller and has very little non-coding DNA.

Chromosomes

There are 46 chromosomes contained in the **nucleus** of body cells:

- Of these, 23 came from the mother's egg and 23 came from the father's sperm
- When the egg and the sperm join together at the time of conception, the first cell of the baby is formed. This cell is copied to make all of the cells of the baby
- The baby's body cells now have 46 chromosomes, made up of 23 pairs, just like the parents (Figure 1.5).

As we age and grow, our cells are continually dividing to form new cells. During this division process, each

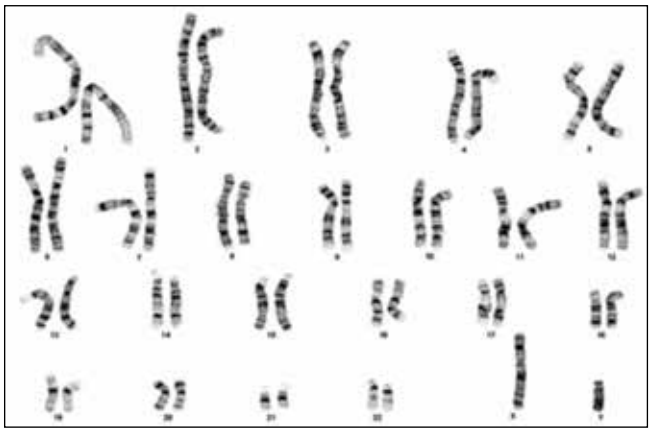


Figure 1.6: Chromosome picture (karyotype) from a male 46,XY.

of the long thin chromosomes coils up tightly, so that each of the 46 individual chromosomes in the nucleus become rod-shaped structures and can be seen when using a microscope.

In a genetic testing laboratory the chromosomes may be coloured (stained) with special dyes to produce distinctive banding patterns and lined up in size order. This produces what we call a **karyotype**. These patterns allow the laboratory to check the size and structure of each chromosome.

Figure 1.6 shows a banded chromosome karyotype where each chromosome has been numbered from the largest (chromosome number 1) to the smallest (chromosome number 22) and arranged in pairs in order of size. These numbered chromosomes are called **autosomes**.

There are two chromosomes that have been given the labels X and Y. These are the **sex chromosomes**. It is these sex chromosomes that determine whether the chromosomes have come from a male or a female.

In females, cells in the body have 46 chromosomes (44 autosomes plus two copies of the X chromosome). They are said to have a **46,XX karyotype**. Eggs (female reproductive cells) are different as they only contain half of the chromosomes (23 made up of 22 numbered chromosomes and an X chromosome).

In males, cells in the body have 46 chromosomes (44 autosomes plus an X and a Y chromosome). They are said to have a **46,XY karyotype**. Sperm (male reproductive cells) are different as they only contain half of the chromosomes (23 made up of 22 numbered chromosomes and an X chromosome *or* a Y chromosome).

Genes

The DNA making up each chromosome is usually coiled up tightly. If we imagine it stretched out, it would look like beads on a string (Figure 1.3):

- Each of these beads is called a **gene**
- Each gene is an instruction for a specific protein
- Thousands of genes make up each chromosome
- Between the genes are segments of non-coding DNA.

Since the chromosomes come in pairs, there are also two copies of each of the genes. The exception to this rule applies to the genes carried on the sex chromosomes, X and Y.

Since men have only one copy of the X chromosome, they have only one copy of all the genes carried on the X chromosome. Women have two copies of the X chromosome in their cells and so they have two copies of all the genes carried on the X chromosome.

To adjust for the fact that women have two X chromosomes with lots of genes while men have only one, one of the woman's X chromosomes is **switched off** or inactivated in each of their cells.

There are very few genes on the Y chromosome and their role is mainly to make a person male, so they are not needed in female cells.

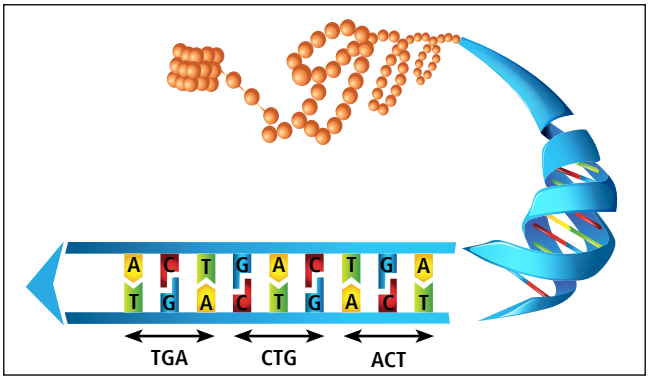


Figure 1.7: The DNA bases pair up to make genes.

DNA

There are over 20,000 genes found in the DNA of each person. Each gene has its own specific location on a chromosome or on the mitochondrial DNA and the genes (coding DNA) plus the non-coding DNA make up that person's **genome**.

- The DNA code is made up of very long chains of four basic building blocks (nucleotide bases) called Adenine (A), Guanine (G), Thymine (T) and Cytosine (C)
- A chromosome consists of two of these DNA chains running in opposite directions. The bases pair up to form the rungs of a ladder twisted to form a double helix (Figures 1.7 and 1.8)
- Pairing of the bases follows a pattern where base A can only pair with base T and base G can only pair with base C. Roughly three billion of these base pairs of DNA make up the human genome

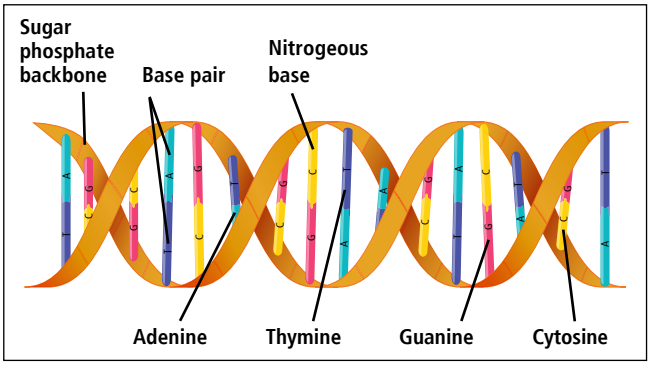


Figure 1.8: The DNA helix.

- Our DNA code is made up of a combination of three of these four chemical 'letters' called a triplet.
  - Each three-letter word (triplet) tells the cell to produce a particular amino acid, the building blocks of proteins
  - The sequence of three-letter words in the gene enables the cells to assemble the amino acids in the correct order to make up a protein
  - Only about 2% of the entire DNA in the human cell is made up of genes that contain the information codes for making proteins
  - The remaining 98% of DNA does not contain the information for proteins and used to be called **junk** DNA. This non-coding DNA separates genes from each other along the chromosomes and there is increasing evidence that it has a role in turning genes **on** and **off**. This non-coding DNA therefore has a control function within the genome.

DNA variations

We all have small variations in our genetic code. That is why we are all unique. Even identical twins have some variations in their DNA by the time they are born. Because we inherit our genes from our parents, members of the same family share their DNA including its variations.

There may be changes in the sequence of letters in the gene message; nucleotide base/s (A, G, T or C) can be missing (called a deletion) or base/s can be added (called an insertion) and these can be of one or many DNA bases.

Variations in the code can occur during our life for a variety of reasons including exposure to radiation, certain chemicals or by chance. Ageing is a common cause of genetic variation. Throughout our lives, our cells are continually being replaced.

Some variations in the genetic information do not seem to make any difference to the function of our cells. These types of DNA variations are quite common.

Other DNA variations can be associated with an increased **chance** of a health condition, for example diabetes or cancer.

Some DNA variations can mean the gene instruction is incorrect so a faulty protein is made or the control switch is changed. A variation in a gene that creates a fault is called a **pathogenic variant** or **mutation**.

A DNA mutation can cause a problem for one cell type but not another, since not all cells use all of the possible proteins.

When a DNA change causes a faulty protein in cells that need that protein, it usually results in disease symptoms that can sometimes be recognised as a genetic condition.

Since we have two copies of each gene, if one copy has a mutation and the other copy is working, then we may not develop any problems.

We are all born with DNA mutations and sometimes these can be beneficial or cause no problem.

When a gene variation is present in egg or sperm cells, it can be passed on to children (inherited).

In other cases, a new gene variation can arise in an egg or sperm cell. This is called a ***de novo*** change.

The person arising from that egg or sperm cell will be the first in the family to have the DNA change which may then be passed down to his or her children and future generations.

Genes contain recipes for the body to make proteins – the Book of Life is like a recipe book for our bodies.

Centre for Genetics Education (10 June 2016).
Fact Sheet 1 – An Introduction to DNA, Genes and Chromosomes.
Retrieved from www.genetics.edu.au on 19 September 2017.

THE HUMAN GENOME

A fact sheet from the National Health and Medical Research Council

The human genome consists of the complete set of human genetic material that is contained in a human cell. In most human cells, the genetic material is made up of long DNA strands that are packaged into 23 pairs of chromosomes. In contrast, eggs and sperm have 23 unpaired chromosomes that parents pass on to their offspring. The offspring then inherit one copy of each chromosome from each parent and this means that siblings have, on average, about half of their DNA in common. More distant relatives have less DNA in common. For example, on average, first cousins have in common about one eighth (12.5%) of their genetic material.

Humans have two kinds of chromosomes: sex chromosomes (X and Y) and autosomes. Of the 23 paired human chromosomes, 22 are autosomes and one is the sex chromosome. The paired sex chromosome in females are two X chromosomes, whereas males have one X and one Y chromosome.

Each chromosome is an organised structure that contains DNA. DNA contains the instructions for building different parts of the cell and body. The instructions are in the form of a chemical code (the genetic code), made up of sequences of four building blocks known as nucleotide bases. The four bases are always paired in DNA molecules, with adenine (A) always paired with thymine (T) and guanine (G) always paired with cytosine (C) to make base pairs.

The human genome inherited from each parent is made up of over 3 billion DNA base pairs. Genes are formed from DNA base pairs that are arranged in sequences and instruct the cell to build the proteins that make up the human body. The genes also contain the coding regions of the human genome that are known collectively as the exome. There are approximately 20,000 genes in humans and these represent only 1-2% of the human genome.

WHAT IS THE RELATIONSHIP BETWEEN DNA MUTATIONS AND GENETIC CONDITIONS?

A genetic disease or condition is caused by one or more genetic changes, which scientists refer to as mutations. A mutation is a permanent change in the DNA code. Inherited mutations are those that are passed on to children from a parent and are called germ line mutations. Some of these mutations occur spontaneously, for unknown reasons.

Mutations also build up in a person's DNA over their lifetime (for example, DNA damage due to sun exposure). These mutations are not passed on to children and are called somatic mutations.

Changes in the DNA sequence do not always lead to health problems because some mutations occur in DNA that is not a part of a gene. Even so, studying these types of mutations can be useful in other types of genetic research.

WHY IS GENETIC TESTING A POTENTIALLY POWERFUL TOOL IN MEDICINE?

Mutations in inherited genes can result in genetic diseases or conditions that may cause problems at any stage of life, depending on the type of mutation. On the other hand, some genetic changes do not cause health problems for the individual but may cause health problems for their children.

Genetic testing examines the genes of an individual and looks for mutations. This information can be used to work out the future possibility of a disease or condition developing for that person or the future risk of a disease or condition in that person's children.

Many diseases are thought to be genetic in nature. However, genetic tests are usually only recommended when there is a history of a genetic health problem in an individual or the family.

Blood relatives share regions of their DNA with each other. If one member of a family is found to have a genetic mutation, other members of the family may have the same mutation. If the mutation causes health problems, then the health of other family members could be at risk. Doctors usually encourage people to share this type of information with their family so that other members can seek medical advice.

National Health and Medical Research Council (November 2013). *The human genome.* Retrieved from www.nhmrc.gov.au on 19 September 2017.

GENETIC DISORDERS

FACT SHEET OVERVIEW FROM BETTER HEALTH CHANNEL

Summary

- A genetic disorder is caused by an altered gene or set of genes.
- The four broad groups of genetic disorders include single gene disorders, chromosome abnormalities, mitochondrial disorders and multifactorial disorders.

Genes are the instructions for the growth and development of our bodies. A genetic disorder is caused by an altered or faulty gene or set of genes. The four broad groups of genetic disorders are single gene disorders, chromosome abnormalities, mitochondrial disorders and multifactorial disorders.

Single gene disorders

Genes are paired – one copy of each gene pair is inherited from the mother and the other copy from the father. Around 6,000 known genetic disorders are caused by inheriting an altered gene.

Generally, the alteration (mutation) means that the information contained in the particular gene is either changed or absent. The four main ways of inheriting an altered gene are:

- **Autosomal dominant** – the alteration is present in every generation and may cause the condition in every person who has the alteration. This is because the altered copy of the gene is dominant over the healthy copy. Examples include Huntington's disease and familial hypercholesterolaemia (genetically linked high cholesterol levels).
- **Autosomal recessive** – the affected person has two copies of the altered gene (they have inherited an altered copy of the gene from both parents). They develop the disorder because they do not have a functioning copy of the gene. Examples of autosomal recessive genetic disorders include cystic fibrosis, phenylketonuria (PKU) and sickle cell anaemia.
- **X-linked dominant** – this type of disorder generally occurs in females. The 'X' refers to one of the sex chromosomes that decide gender. The mother always provides an X, while the father provides either X (female child) or Y (male child). Women with an X-linked dominant disorder have one altered copy and one normal copy of a gene that is on the X chromosome. An example of an X-linked dominant genetic disorder is a rare form of rickets known as hypophosphataemic or vitamin D resistant rickets.
- **X-linked recessive** – this type of disorder is more common in males. It is caused by an alteration in a gene on the X chromosome. Since a male has one X and one Y (XY), he does not have a second 'healthy' copy of the gene. Examples of X-linked recessive genetic disorders include Duchenne muscular dystrophy and haemophilia.

Chromosome abnormalities

Genes are the body's instructions for making different molecules (such as proteins or hormones). The estimated 23,000 genes that make up a human being are arranged along tightly bundled strands of a chemical substance called deoxyribonucleic acid, or DNA. The DNA strands are tightly packed into structures called chromosomes. Over 1,000 known disorders are caused by chromosome abnormalities.

A chromosome disorder means there is a change in either the structure or the number of chromosomes. This can happen in three main ways:

- The altered chromosome is passed from the parent to the child
- The abnormality happens when either the sperm or egg (germ cells) is created soon after conception.

Chromosome abnormalities can occur in various ways, including changes in the number or structure of chromosomes, or how they are inherited.

Changes in number of chromosomes

Most people have 23 pairs of chromosomes, or 46 chromosomes in all. When the egg or sperm is made, the pairs split so that each egg or germ cell only contains 23 chromosomes.

Occasionally an error occurs during the division: for example, the egg or sperm might be missing a chromosome (22 chromosomes) or have an extra one (24 chromosomes), so at conception the baby has either too few (45) or too many (47) chromosomes.

A well-known example of this type of genetic disorder is Down syndrome, where a person has 47 chromosomes rather than 46.

Babies are rarely born with changes in chromosome numbers because most of these pregnancies end in miscarriage.

Changes in chromosome structure

Sometimes the information contained in a chromosome breaks up and the pieces reform in a different pattern. For example, a fragment of chromosome may break off and be lost during the formation of either the egg or sperm cell. A section of chromosome might also break away and 'stick' to another chromosome.

In other cases, a fragment of chromosome may copy itself or the ends of the chromosome may join to form a ring. Some changes in structure are 'balanced' (chromosome material is not lost or gained) and are unlikely to result in a genetic disorder.

Uniparental disomy

Uniparental disomy means the child inherited a particular gene pair (both copies of the gene) from one parent only. This can cause a disorder if it is necessary for the child to have inherited one such gene from each parent.

Chromosomal mosaicism

Normally every cell in the body contains the same genetic information – all 46 chromosomes, designated as 46XX (female) or 46XY (male). A person who has chromosomal mosaicism has different numbers of chromosomes in different cells; for example, 46 in some cells and 47 in others.

Mitochondrial disorders

Mitochondria are like little batteries that make energy within each cell. The energy source is a chemical called adenosine triphosphate (ATP). Organs like the brain, heart and liver can't survive without ATP.

Genes within the mitochondria, as well as in the nucleus of the cell, instruct the cell on how to make the enzymes that are crucial to ATP production. If any of these genes are altered, this can affect enzyme production and interfere with the production of ATP. If one of the genes in the mitochondria is altered, then the condition is inherited only from the mother. This is because each person inherits their mitochondria only from their mother, and not from their father.

The symptoms of a mitochondrial disorder, depending on the genes involved, can affect the:

- **Brain and spinal cord**– intellectual disabilities, deafness, vision problems and seizures
- **Heart** – cardiomyopathy (heart failure) and irregular heartbeat disorders
- **Musculoskeletal (locomotor) system** – poor muscle tone and floppiness.

Multifactorial disorders

Multifactorial (involving several factors) disorders, such as many common birth defects or diseases like high blood pressure, are disorders caused by the environment interacting with the action of several genes. (This is also sometimes called polygenic inheritance.)

For example, the birth defect spina bifida is caused by the action of several genes and also depends on the amount of folate in the mother's diet during pregnancy (the environment). High blood pressure is influenced by a large number of genes, but also is influenced by a person's diet and salt intake.

Where to get help

- Your doctor
- Victorian Clinical Genetics Services (VCGS), Royal Children's Hospital Tel. (03) 8341 6201
- Cancer Council Victoria, Information and Support Service Tel. 13 11 20

This page has been produced in consultation with and approved by Victorian Clinical Genetics Services (VCGS).

State of Victoria (June 2014). *Genetic disorders*. Retrieved from www.betterhealth.vic.gov.au on 19 September 2017.

HUMAN GENOMICS IN GLOBAL HEALTH: GENETIC TESTING

THE WORLD HEALTH ORGANIZATION EXPLAINS SOME OF THE ETHICAL, LEGAL AND SOCIAL IMPLICATIONS ARISING FROM THE USE OF GENETIC TESTS

GENETIC TESTING

The role of genetics and the environment in the onset of many major non-communicable diseases, particularly monogenic diseases, is well established. Consequently, genetic testing is gaining recognition for the many advantages it has to offer in the prevention, management and treatment of disease. Among their many uses, genetic tests most commonly present an opportunity for individuals to become informed about their genetic predisposition to disease, and for couples to be aware of the possible genetic characteristics of their unborn children. Stemming from the informative potential of genetic testing some critical ethical, legal and social issues come to the forefront.

THE INDIVIDUAL'S RIGHT TO CHOOSE

In an effort to reduce genetic diseases, especially those peculiar to certain populations, many communities encourage couples to perform genetic testing prior to marriage as well as on the fetus during pregnancy, to determine any risk of disease. While this strategy has effectively reduced the prevalence of some genetic diseases like thalassaemia, for which there is still no cure, it is argued by some that it limits the individual's freedom of choice.

Couples may be coerced into genetic testing with little regard for obtaining their free and informed consent. This is particularly true for women who are often under pressure to conform to their family decisions. For example, a few countries require couples to undergo testing for thalassaemia prior to marriage. Though couples are not forced to act upon any knowledge of risks, there is considerable social pressure to prescribe to advocated medical interventions. The pressure is twofold as the couple is first compelled to get tested, and then to act a certain way in light of the diagnosis. This is especially so in low- to middle-income countries where treatment is expensive, not many options are available for parents, and the termination of a pregnancy may be viewed as the most practical response in economic insufficiency.

On the other hand genetic tests may provide individuals, who seek them freely, with information needed to make important decisions about their future, therefore supporting their right to make a informed choice.

CONFIDENTIALITY

As with other areas of clinical medicine or science, confidentiality is important in genetic testing. If anything, the confidentiality of genetic information may need to be guarded even more stringently than in the ordinary case.

Genetic tests give an assessment of an individual's inherent risk for disease and disability. This predictive power makes genetic testing particularly liable for misuse. Employers and insurance companies have been known to deny individuals essential health care or employment based on knowledge of genetic disposition. This type of discrimination can be socially debilitating and have severe socio-economic consequences. It is important, therefore, to ensure the confidentiality of test results, and to establish legislation permitting only selective access to this information.

Genetic information can have important implications not only for the one who is tested, but also for her relatives. Respecting a patient's confidentiality by not disclosing the results of a genetic test to third parties can therefore conflict with the wellbeing of family members, who could benefit from this knowledge. Finding the right balance between the patient's privacy and confidentiality of her genetic information, and what is in the best interests of family members, is an ongoing ethical and social challenge.

STIGMATISATION AND DISCRIMINATION

Knowledge of genetic risks can lead to potential social and psychological consequences for the individual. Socially, knowledge from genetic tests may lead to stigmatisation and discrimination within the community. Refusing to undergo genetic testing as well as choosing to undergo genetic testing can both lead to discrimination and stigmatisation depending on the prevalent social norms regarding acceptance and use of the technology.

Further, knowledge of test results may lead to the marginalisation of the individual from mainstream society by virtue of the health risks identified.

Discrimination can be in the form of denial of health insurance, employment or simply social acceptance. In particular, knowledge of risk of disease may be used by health insurance providers and employers to deny individuals employment, benefits and allowances and medical coverage or health insurance. This is especially worrisome in communities that rely heavily on private insurance systems as a source of funding for necessary medical treatments.

On the other hand, within the context of a well-informed community integrated clinical and social support systems which include counselling services for patients and their families, knowledge of genetic disease or predisposition can lead to better care and management of the patient and ultimately to improved quality of life.

World Health Organization (WHO). *Human Genomics in in Global Health.* Retrieved from www.who.int on 19 September 2017.

MEDICAL GENETIC TESTING: HEALTH INFORMATION FOR YOU AND YOUR FAMILY

A resource developed by the National Health and Medical Research Council

PART 1 – THE BASICS

DNA, genes and chromosomes

The human body is made up of millions of cells. Most cells in your body carry a complete set of DNA or deoxyribonucleic acid. DNA provides your cells with the information or codes needed to make your body work and grow. DNA is also responsible for determining many of your characteristics, such as your hair and eye colour.

DNA is arranged into structures known as chromosomes. Every human cell contains 46 chromosomes, arranged in 23 pairs, with one member of each pair inherited from each parent. Of these 23 pairs, 22 pairs are 'autosomal chromosomes', which have the same structure in both men and women. The final pair is composed of the X and Y chromosomes, which are known as the 'sex chromosomes'. Males have one X and one Y chromosome, whereas females have two X chromosomes. Genes are sections of DNA that are carried on chromosomes.

DNA, you and your family

Because you inherit your DNA from your parents, the genetic information your DNA contains may also be shared by other family members. This is why families often share similar physical characteristics. Despite sharing DNA with your family, you are still unique – even identical twins develop some differences in their DNA during pregnancy, making each unique when they are born.

Genetic variations, mutations and health

Within your DNA there are many small differences or variations in the code. Most of these variations don't affect the way your body works. In fact, it is these variations that make you unique.

Unlike DNA variations that are present in the egg or sperm cells (known as 'germ' cells), variations that occur in body (or 'somatic') cells, affect only the cells of that tissue, e.g. a breast or skin cell. Somatic variations cannot be passed from parent to child.

Everyone has mutations; mutations are variations in your DNA that are not part of the standard variation that occurs normally in people. Some of these mutations can affect your health by:

- Directly causing a genetic condition
- Leading to a change in your risk of developing certain health conditions, and/or
- Affecting how you react to outside factors, such as medicines.

DNA variations also build up in our cells as we age and may affect the usual way that cells grow. These variations are copied when cells replicate and may cause cells to grow out of control and form a tumour (cancer). However, it is important to remember that not all mutations are bad. In some cases, a mutation can help protect against certain conditions.

As genes come in pairs, you can have one copy that is faulty while the other copy is working as it should. In such cases, you may or may not have or develop a condition. It depends on whether one working copy of the gene is enough to keep your body working as it should. Even though you may not have a condition, you can still be a 'carrier' of the faulty gene and may pass it onto your children. If you are a carrier, your children may be at risk of the condition you carry, particularly if there is a chance that they can inherit two copies of the same faulty gene (one from each parent).

Where one faulty gene directly causes, or indirectly affects susceptibility to a health condition, and that gene is passed from parent to child there is a family history of the condition. That is, it is said to 'run in the family'.

PART 2 – GENETIC TESTING

Genetic testing and health information

Medical genetic tests look for variations in your DNA sequence, since these variations provide important information about your health. This information can be about your current or future health, the health of your child, or that of your developing baby during pregnancy. Because of this, genetic testing results can help you make important decisions about your lifestyle and family planning.

For example, finding out that you have inherited a mutation that puts you at increased risk of certain cancers can help you manage your health. It can allow

you to access options such as screening or early treatment to prevent the development of cancer. However, for some genetic conditions, such as Huntington Disease, there currently is no prevention or cure. Genetic testing results can therefore return mixed news, and it is important to consider this when making your decision about whether to get tested.

Deciding whether to get tested

As we share our DNA with our genetic relatives, your genetic testing results can have implications for other family members. Therefore, doctors who refer you for genetic testing must take into account not only the technical and scientific aspects of a test, but also the wider implications that it can have on your family. To make an informed decision about taking a genetic test, your doctor can help you in a number of ways, including:

i) Determining the right test for you

After talking to you about your health and family history, asking about your symptoms, and perhaps drawing a family tree (sometimes called a pedigree), your doctor might suggest that you consider having a specific kind of genetic test.

Types of genetic tests available include:

- **Diagnostic tests** – used to confirm a diagnosis if you have symptoms of a condition
- **Genetic carrier tests** – used to show whether you are a carrier of the variation causing a genetic condition
- **Predictive tests** – used if you have a family history of a genetic condition to show whether you have inherited the faulty gene that directly causes, or puts you at increased risk for the condition, before signs or symptoms appear
- **Prenatal tests** – used if you are pregnant to find out whether your unborn child will be affected by, or develop a particular condition
- **Pharmacogenetic tests** – used to help determine the type or dose of a medicine that is best for the treatment of certain conditions.

ii) Providing information, advice and support

It is important to have all the information you need before you decide whether to undertake a genetic test. Your doctor may advise you to also see a genetic counsellor, or refer you to a clinical geneticist or genetic service. Professional advice can help you and your family to think about the medical, emotional and ethical factors that could affect your decision.

Things to consider in making a decision to be tested:

i) What is known about the condition for which testing will be done?

Factors include:

- How the condition could affect your health, lifestyle and family
- Whether the condition can be prevented or whether any treatments are available, and what they are
- Current understandings about whether the condition is inherited and how this occurs
- The availability of information and contact details of support groups or organisations that can give you more information about the condition and support for it.

ii) What does the test involve?

Factors include:

- How many appointments will be needed
- Details of the costs involved (if any)
- Details about the testing process (including the kind of sample that is needed, e.g. a cheek swab or saliva sample, and how it will be taken)
- How long it will take to get the results.

iii) What are the benefits and risks of genetic testing?

Possible benefits can include:

- Reducing or putting an end to uncertainty about your future and/or your child's future if you are at risk of a genetic condition
- Helping you to make informed choices about your future (e.g. to get treatment; to plan having

children; to make lifestyle choices to lower your chance of getting the condition, or to have regular screening tests to detect early signs of the condition), and/or
- Confirming that a faulty gene is not present (and that you don't have a certain condition) providing you with relief, and your doctor with more information to help uncover the cause of any ill-health.

Possible risks can include:
- Raising anxiety, especially while you are waiting for results
- Receiving results that may cause distress, particularly if they are not clear-cut, or if they show that you have or will get a condition that currently can't be treated
- Causing tension and complications within family relationships if testing in families is not carefully managed (e.g. family members that find they have the faulty gene may feel overwhelmed, angry or resentful, while others who do not may feel guilt)
- Receiving results that may involve and/or reveal information about close genetic relatives, including unwanted information (e.g. about paternity, maternity, adoption or children conceived with donated eggs or sperm), and/or
- Implications for life insurance.

Outcomes of the genetic testing process

What happens to your DNA sample and results?

Once your sample has been taken, the DNA it contains is removed and analysed in a specialist laboratory. When testing is complete, the test results are sent to your doctor. Some laboratories keep your DNA for a period of time, so that the result can be checked if necessary.

What do the results mean?

When considering your genetic test result, it is important to remember that genetic test results have a few features that make them different from other health tests:

1. **They're not just about you** – your genetic test results may also reveal information about your relatives. If you have inherited a faulty gene, there is a chance you will pass it on to your children. It may also be present in other relatives (e.g. brothers, sisters and cousins).
2. **They don't always tell the whole story** – some genetic test results, such as a test for Huntington Disease, can be very precise and identify with great accuracy that an individual has or will develop a genetic disorder. However, your environment and lifestyle can also impact on your health. So, with some DNA genetic tests, there are still limitations on our current understanding of how a test result might affect your risk of developing a particular condition.
3. **They are not always concrete** – many test results can only indicate the likelihood of risk, such as with breast cancer (BRCA1 and BRCA2 gene tests). Where a gene variation results in an increased risk of developing a condition, the condition will only develop if another 'environmental' factor is present as a trigger. Though a test result may tell you that you are more likely than average to develop the condition associated with that faulty gene sometime in your life (referred to as a 'positive' result), it doesn't always tell you that you will definitely get it, nor when, or how severe it will be. Furthermore, a 'negative' result may not guarantee that you won't develop the condition.

Your doctor can help you to understand your results and what they mean for you and your family.

Access to your results

In some ways, your genetic test results are like those of any other test. Your doctor discusses them with you and your confidentiality is assured. But because DNA is shared within families, your doctor may ask you to talk to your genetic relatives about your results if the results indicate that your genetic relatives may also have inherited the faulty gene. Similarly, while your non-genetic relatives (e.g. spouses, partners or those related by marriage) are not at personal increased risk of the condition, it may be appropriate to discuss your result with them, particularly if your present or future children could inherit the condition or the increased risk.

You can speak to your family yourself, or ask your doctor or genetic counsellor to tell your family on your behalf. In some cases, it may not be necessary for you to be identified if you don't want to be. If your genetic relatives know they may be at increased risk, they can choose for themselves whether to be tested, just as you did.

Disclosure of information to genetic relatives without your consent

The *Privacy Act 1988* (Commonwealth) applies to health professionals in the private sector. Similar legislation exists in the States and Territories that apply to those working in the public sector. These laws prohibit health professionals from disclosing personal information without your consent.

Changes to the Commonwealth *Privacy Act* made in 2006 affect the disclosure of relevant genetic information by private health professionals. This only applies in cases where your genetic test result indicates that there is a serious risk to genetic relative/s, and you do not inform them or consent to them being informed of that risk. Under these rare circumstances, a private health professional may disclose this information to your genetic relative/s. However, this can occur only in cases where such disclosure is considered necessary to lessen or prevent a serious threat to the life, health or safety of your genetic relative/s.

Doctors working in the public health system were not affected by this change and are currently not able to disclose any information to your genetic relatives without your consent. This issue is under review by State and Territory governments.

Implications for insurance

Life insurance is based on an assessment of the risk that

you will make a claim because of the onset of an illness or death. Life insurance is described as risk-rated insurance. The assessment is based on information that you have about your family and personal history of illnesses. The assessment also considers aspects of your lifestyle that may have an impact on your future health, such as whether you smoke. This information becomes part of the overall assessment of your application, but is not passed on to anyone else.

By law, insurers are able to discriminate on the basis of the information provided, as long as their assessment is reasonable. That is, discrimination is lawful as long as it is based on appropriate statistical (e.g. scientific) data. This means that some people will have to pay more than usual for their policy or even be unable to obtain cover for life insurance products.

In Australia, when you apply for life insurance, you are currently not required to have a genetic test. But if you have had a test and know the results, you are required to tell the insurance company, just as you need to tell them all the other relevant information.

Unlike life insurance, health insurance in Australia is based on community rating. Health insurance does not involve individual risk rating, therefore disallowing any legal discrimination of an individual by health insurers.

Do all genetic tests need to be ordered through a doctor?

A growing number of genetic tests are available direct to the public, often over the internet. Known as direct-to-consumer (DTC) genetic tests, these usually involve scraping a few cells from inside the cheek and mailing the sample to the company. The company's laboratory analyses the sample and sends the results directly back to you.

DTC tests are relatively simple and can allow you an opportunity to take a greater interest and responsibility in your own health. The test might also appeal to your curiosity to discover what makes you unique. However, it is important to know that there are potential problems and risks associated with any genetic testing, as already mentioned.

One key issue is that the usefulness of a test result depends on correct laboratory processes being followed and on accurate interpretation by a health professional. However, health professional involvement can be limited in the DTC process. Regulation of DTC testing laboratories, which are often located offshore, is difficult and interpretation of results can also be complex. Special training is required to be able to analyse genetic test results and to understand how they apply to you and your situation.

Doctors, clinical geneticists and genetic counsellors have an important role in giving you support and information before, during and after genetic testing. If you are considering having a DTC genetic test, it's a good idea to discuss this with your doctor or a genetic counsellor first.

More information on the DTC process, including risks and benefits, is also available in *Understanding Direct-to-Consumer (DTC) DNA Genetic Testing: An information resource for consumers*, which is available on the NHMRC website (and reproduced on the next page of this book).

What about testing in children?

There are many different things to think about with any sort of genetic testing in children, especially when the child is too young to understand their results and you are making decisions on their behalf.

We don't know enough about the impact on children of knowing that their lives may be seriously affected by a genetic condition sometime in the future. For this reason, the Human Genetics Society of Australasia recommends that parents consider having their children tested only when the result is likely to directly benefit the child's health during childhood – relieving uncertainty or anxiety within the family is not considered a valid reason.

Where can I find more information and support?

The diagnosis of a genetic condition can place a lot of pressure on a family. Support is available for families and individuals who are affected by genetic conditions.

Ask your doctor, genetic counsellor, clinical geneticist, or clinical genetic service for more information or visit the Genetic Alliance Australia website at www.geneticalliance.org.au for more details on available support services.

Remember ...

- It is important that you fully understand the benefits and risks before you consent to testing. If you want to know more, keep asking questions. Don't rush the decision.
- Your doctor or genetic counsellor can help you think things through and give you the information you need to make an informed decision.
- If you think it will help, talk about it with your family, particularly those who may also be affected by the results.
- If you're still not sure, discuss alternatives, such as postponing the test, or get a second opinion.
- Testing is voluntary. You can pull out from the testing process at any stage. Even after the testing has been done, you can decide not to find out your results.
- People have many different reasons for being tested, and the decision is easier to make in some situations than in others. Ultimately, having a genetic test is your decision to make.

National Health and Medical Resesarch Council (NHMRC). *Medical Genetic Testing: Health information for you and your family.* Retrieved from www.nhmrc.gov.au on 22 February 2018.

UNDERSTANDING DIRECT-TO-CONSUMER GENETIC DNA TESTING

AN INFORMATION RESOURCE FOR CONSUMERS, COURTESY OF THE NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL

Direct-to-consumer (DTC) genetic tests can be purchased directly by you, often without the involvement of your doctor. DTC genetic tests can be used to establish parentage or to trace one's ancestry. Some DTC genetic tests may also have health implications.

In recent years, there has been a significant increase in the number of DTC genetic tests that you can purchase. NHMRC has developed this information resource to help you better understand this type of testing.

What is a DTC genetic test?

DTC genetic tests are usually purchased over the internet. You will be asked to send a sample such as saliva or a swab from the inside of your mouth to a laboratory. The laboratory will extract DNA (your genetic material), analyse the sample and provide the results directly to you, often without the involvement of your doctor.

Important issues to consider if you are planning to purchase a DTC genetic test

You might like the idea of DTC genetic tests because they don't involve a blood test, are simple to do and can allow you to keep the results private. Such a test might also appeal to your curiosity to discover more about yourself. Whatever the case may be, it is important to know that while DTC genetic tests can be taken for fun or personal interest, there are factors such as test accuracy and privacy, which you should consider if you, or someone you know, is thinking about having a DTC genetic test.

Are DTC genetic tests accurate?

The NHMRC encourages individuals interested in undertaking a DTC genetic test to exercise caution. Companies offering DTC genetic tests are mostly located overseas, even if the initial delivery address is within Australia. All medical testing laboratories in Australia are required to be accredited. To ensure quality and reliability, you should ensure that overseas laboratories are accredited to international standards equivalent to the Australian standards. Some DTC genetic tests also come with disclaimers that release the company from responsibility for inaccurate test results. You should carefully read the terms and conditions of your chosen DTC genetic testing company.

Medicare benefits are not available for DTC genetic tests.

How useful are DTC genetic tests?

Your DNA is inherited from your parents and it contains genetic information that contributes to your development and how you function. DTC genetic tests look for specific variations (changes in your DNA) which have been linked to diseases or personal characteristics. There are many variations that are yet to be understood. In the case of tests that claim to assess your risk of developing a particular disease, the variations tested often only have a small influence on your overall risk of developing a disease. This is because your genes are not the only things that determine your future health, and even genetic tests that meet high quality laboratory standards may not provide you with any medically useful information. Lifestyle, environmental factors and normal ageing have an important influence on your risk of developing a disease.

Before undertaking any genetic test – DTC or not – it might be worthwhile to consider whether the information the test provides will make a difference to you. Is there something that you hope to be able to do after getting the test result that you can't do now? In the case of health-related predictive tests, for example, unless you are willing to make changes to your lifestyle based on the test results, such tests may not be of much benefit to you.

If you have a concern about your current health status or how it might change in the future, consult your doctor.

Your doctor will be able to give you advice on the most appropriate tests for you. For example, standard, non-genetic clinical tests, such as tests to measure cholesterol levels, can already provide you with a good indication of your future risk of heart disease.

Talking to your family can also be a useful way of finding out more about your family's medical history. Should you have a family history of a condition you are concerned about, speak to your doctor.

If genetic testing is suggested by your doctor you will be referred to a clinical setting in Australia. You will be provided with genetic counselling and doctors will interpret the results of your testing. More information on this kind of testing, known as medical genetic testing, is available from the NHMRC website.

DTC genetic tests should not be used as the sole basis for clinical decision making and health care.

Protection under Australian law is limited for purchase of DTC genetic tests

Australian law protects your privacy rights for services provided in Australia, but these protections do not apply to overseas services.

Some DTC companies also sell information about you and your genetic results to pharmaceutical and other companies. It is important to understand that DTC genetic testing companies may ask if your sample and results can be used for other purposes, such as research.

You should carefully read the privacy policies and terms and conditions to make sure these are acceptable to you.

Possible implications for obtaining risk-rated insurance

In Australia private health insurance is not "risk-rated". This means that everyone can access health insurance and that insurers cannot discriminate on the basis of health status, claiming history or other factors.

However, products such as life insurance or income protection insurance are "risk-rated". When applying for such risk rated insurance products, you have to declare whether you have any conditions that may increase your health risks. You are also required to declare whether you (or your immediate biological relatives) have had any genetic testing for which the result is known. This is another reason why you need to be confident in the quality and accuracy of any genetic test that you have. You should make sure that the testing laboratory is accredited to Australian (or equivalent international) standards.

Possible implications for your family members and certain groups

Obtaining your own genetic test results may reveal unexpected information about you and your blood relatives. Similarly, genetic test results on your blood relatives may reveal information about you. You or your relatives may or may not wish to know this information. You may wish to discuss this with your family and relatives. It is important to consider this before you access DTC genetic testing.

There may also be social, cultural and legal issues that need to be considered for certain groups. For example, Aboriginal and Torres Strait Islander Peoples believe that information about heritage is often collectively owned. In this situation, a decision to be tested may have implications for an entire community.

What if you have already purchased a DTC genetic test?

DTC genetic tests that are not medically relevant (such as tests of your ancestry) can be a source of interesting information. However, if your DTC genetic test result includes any medically relevant information, you should visit your doctor with the results and tell him or her why you wanted to have the test done. Your doctor can then decide whether further action is needed. This may include actions such as repeating or confirming the genetic testing in another accredited laboratory, referral to a genetics specialist or genetic counsellor, or arranging for additional non-genetic tests.

Additional information on genetics:

- *Direct-to-Consumer Genetic Testing: A Statement from the National Health and Medical Research Council (NHMRC),* www.nhmrc.gov.au/guidelines/publications/g9
- *Medical Genetic Testing: Health information for you and your family*, www.nhmrc.gov.au/guidelines/publications/ps3
- *Use and disclosure of genetic information to a patient's genetic relatives under Section 95AA of the Privacy Act 1988 (Cth) – Guidelines for health practitioners in the private sector*, www.nhmrc.gov.au/guidelines/publications/pr3
- *Discussing Direct-to-Consumer Genetic DNA Testing with Patients: A Short Guide for Health Professionals*, www.nhmrc.gov.au/guidelines/publications/g7
- *The Provision of Direct-to-Consumer Genetic Tests: Guiding Principles for Providers*, www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-geneticstestguide

National Health and Medical Research Council (December 2014). *Understanding Direct-to-Consumer Genetic DNA Testing – An Information Resource for Consumers.* Retrieved from www.nhmrc.gov.au on 22 February 2018.

WHY WE SHOULD TEST EVERYONE'S GENES TO PREDICT DISEASE

If we could test the genome of all Australians we could better target preventive health campaigns, assert Anna Vinkhuyzen and Naomi Wray

If you could take a test that would reveal the diseases you and your family might be more likely to get, would you want to do it?

Rapid developments in gene testing technologies have sparked debate about whether healthy Australians should undergo genetic testing.

A bit about genetic testing

First we have to understand the difference between the genetic tests we're talking about. There are three key applications of genetic tests and they're often confused.

The first application is a diagnostic test – where someone is ill and we use a genetic test to try to find out what's wrong with them.

The second type is when a family member has a genetic disease and you want to know if you carry the same mutation that made them ill (predictive test).

The third type of genetic test is for genetic "risk prediction". This can be used on anyone, in the absence of illness, to find out whether they carry genes that could lead to illness later.

The first two types are typically available for a small number of diseases and each test is for a faulty copy of a single gene. Most of these diseases are very rare and many start in childhood. For diseases where diagnostic tests are available these are valuable to confirm diagnosis.

Predictive tests are worth conducting when they could lead to direct action to avoid disease (for example, removing breast tissue in the presence of a faulty copy of the BRCA1 gene).

Diagnostic and predictive genetic tests for some very rare diseases have been available for decades. These tests could have implications for coverage and cost of health and life insurance.

The case for testing the healthy

Genetic tests that predict your risk for more common diseases may soon become readily available in the healthcare industry. These could help doctors diagnose disease, and could prompt lifestyle changes in patients in the same way a cholesterol test serves as a risk predictor for heart disease.

Obtaining the DNA blueprint for an individual is cheap, costing no more than A$50 per person.

The results from large-scale disease studies are then applied to this blueprint and we can estimate a person's genetic risk for many common diseases. Despite inaccuracy in the genetic risk predictor for any one individual, these predictors can be informative at a group level. This is where genetic risk prediction becomes very attractive.

Imagine we have the genetic blueprint for all Australians. We could then stratify people into high-risk versus low-risk groups for numerous common diseases. Disease prevention programs such as mass screening for breast cancer and bowel cancer are currently targeted at defined age groups, with age being the only indicator of risk. Using genetic risk prediction, these programs could be aimed at those who are at high genetic risk for the disease.

Imagine a disease that affects 1% of the population. Let's say the genetic risk predictor indicates only 20% of the population is at increased genetic risk and we invite those people for clinical screening. In this scenario, still the vast majority of those screened will not get the disease. But of those who will get the disease, most are expected to have been selected for the screening

Imagine we have the genetic blueprint for all Australians. We could then stratify people into high-risk versus low-risk groups for numerous common diseases.

A major impediment of a genetic risk prediction test for common diseases is that it can't be used as a diagnostic instrument because it has low accuracy ... In common diseases, not one but thousands of genes are involved.

program based on their genetic risk prediction test.

This example shows how screening only those at high genetic risk following a genetic risk prediction test will lead to more cost-effective mass screening programs and could prevent overdiagnosis and over-treatment.

Genetic risk prediction becomes even more useful when linked to other sources of health data – such as medical history, family medical history and lifestyle factors such as smoking. Ongoing research is expected to improve accuracy of genetic predictors for common diseases.

The potential for applying these predicted risks in public health programs and clinical settings is huge. This means we could base our healthcare system on prevention rather than treatment. And, when someone does fall ill, we could more accurately target their specific causes and symptoms using precision medicine.

What needs to be addressed first?

A major impediment of a genetic risk prediction test for common diseases is that it can't be used as a diagnostic instrument because it has low accuracy. Existing tests for rare genetic diseases are straightforward and accurate because they test for a faulty copy of a single gene. The presence of a faulty copy is often conclusive.

In common diseases, not one but thousands of genes are involved. Each single gene has a small individual contribution to disease risk. Also, non-genetic factors, such as lifestyle habits, contribute to the risks of common diseases.

Predicting risk from the small individual contributions of thousands of genes in combination with non-genetic factors is much more complex. This complexity makes it impossible to predict an individual's risk for disease with high accuracy.

Over the past ten years, accuracy of genetic risk predictors for common diseases has improved and further improvement is expected. But due to the complex nature of common diseases, the genetic predictor will never be entirely accurate.

A large number of technical and social challenges need to be addressed for smooth implementation of genetic risk prediction in the healthcare system. In particular, there are concerns about privacy and insurance.

And all genetic testing should come with detailed explanation to ensure people properly understand the risks facing them and can cope with them. Awareness of increased risk for developing a disease can be stressful. On the other hand, people may become proactive in trying to avoid the disease by living a healthier life to reduce their chance of getting sick.

Australia is not alone in facing the challenges of regulation of genetic testing. Once genetic risk prediction is implemented in one country, others will likely follow.

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THE CONVERSATION

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Brace yourself, genetic testing might give you more than you bargained for

Caroline Ford and Orin Chisholm ask: is testing simply hype which offers unsubstantiated hope to consumers, or is it the first stage of patient empowerment over their own health and lifestyle choices?

Drink red wine to prevent cancer. But don't drink too much! Get some exercise. But don't overdo it. Give up, it's all genetic anyway – think of Angelina Jolie!

We are constantly bombarded with conflicting information about our risk of developing cancer. It is difficult to know who to believe, let alone how to respond.

What if you could take a simple test that would reveal your individual risk of developing not only a range of cancers, but hundreds of other diseases? Imagine if it could also tell you which drugs would be most effective for you, if you did develop cancer or other diseases.

The rapidly reducing cost of DNA sequencing has made this one-time fantastical idea an emerging reality. Only 10 years ago it cost about US$10 million to sequence a human genome, so there was little prospect that individuals would, or could, seek out their own unique genetic maps to find out more about their ancestry or their inherited health risks.

Recent advances in genetics mean genetic sequencing is more affordable (US$1,000 to US$3,000) and already guiding treatment across a range of illnesses from cancer to degenerative brain diseases.

New unregulated direct-to-consumer businesses are emerging, making it possible for anyone to order their individual genetic profile by posting off a saliva sample taken at home. But do you really know what you are signing up for?

THE AGE OF PERSONALISED MEDICINE

Personalised medicine means using a patient's genome to both predict their likelihood of developing certain diseases, and to guide which treatments are most likely to be effective in a particular individual. It's also called customised medicine, precision medicine, individualised medicine, bespoke medicine and targeted medicine.

Our genes hold our hereditary information. Every cell in the human body is made up of about 20,000 genes that are passed down from parents to child. Genes contain information that instructs the growth, development and function of the human body. Some genes control simple characteristics such as hair colour and height, others influence complex characteristics such as intelligence. Some genes control how other genes work, telling them when to switch on and off.

We all have alterations, or mutations, in our DNA. Mutations can be passed down from parents to children, or can occur spontaneously, especially as we age. Some are harmless and may determine, for example, whether our ear wax is wet or dry.

However, a mutation in an important gene that prevents it from working properly, or a gene that is missing altogether, can have serious consequences. Early genetic testing focused on debilitating inherited diseases, such as cystic fibrosis and Huntington's disease, that are caused by mutations in single genes. Tests looked only for a known mutation in a specific gene to confirm or rule out the associated condition.

As testing has become more sophisticated, we have been able to extend this approach to more complex conditions such as cancer. Mutations in two genes called BRCA1 and BRCA2 are associated with an increased risk of developing breast and ovarian cancer, and can be inherited within families.

Are we psychologically equipped for these kinds of dilemmas and scientifically literate enough to interpret our own results?

BRCA1 and BRCA2 normally help clean up mistakes in our DNA that our cells can make when they divide, a process called DNA repair. When either of these genes is altered or mutated, this protective function is disabled, leading to uncontrolled replication of cells with mistakes. This can lead to cancer.

The good news is that we can test for these mutations, and patients can then use the results of this test to assess their risk of developing cancer, and make informed choices. This is the same hereditary genetic mutation that prompted Angelina Jolie to have a preventative double mastectomy two years ago, and preventative surgery to remove her ovaries this year.

The other good news is that in recent years scientists have discovered that patients with mutations in BRCA1 and BRCA2 are exquisitely sensitive to some forms of chemotherapy and a second type of drug called a PARP inhibitor. The same mutation that generates the mistakes in these cells can actually make them more responsive to this drug. Decisions about treatment can then be "personalised" to the individual.

WHAT DOES THE FUTURE HOLD?

Currently, health systems in Australia and overseas do not offer patients the option of sequencing their entire genome as a means of identifying and managing future health risks. Today genetic testing is only available in Australia for specific genes, is tightly regulated and is used only when symptoms are apparent, or a genetic risk is likely, such as a close relative developing a particular cancer or condition.

In five to 10 years' time, however, we may be facing very different choices, including the option to look for future diseases before they actually occur.

As many cancers do not appear until middle age or later, a young healthy person might discover they have various elevated risks among the many anomalies a DNA test could throw up. Such results might not be provided by a medical professional, but by a commercial operator, and without genetic counselling to explain what they mean to the individual and their family.

What might the implication be of a high-risk result? Should an individual's relatives be informed, as their risk may also be high, or do they have a right not to know? And what about minors: will parents have the right, or even an obligation, to test babies and children for potential genetic risks, even if medical science offers no prevention or treatment options?

Are we psychologically equipped for these kinds of dilemmas and scientifically literate enough to interpret our own results?

There are currently many reasons to be cautious. First, there are potentially millions of genetic alterations. Most are still not understood. Personalised medicine cannot currently give anyone a comprehensive picture of individual risk simply because far too much remains unknown.

Second, personalised medicine can only indicate elevated risks, it cannot determine whether or not a patient will actually go on to develop a certain type of cancer. Environment and lifestyle also play a big role in our health.

Insurance companies, however, deal entirely in risk. That means genetic profiles could be used to deny higher-risk individuals various types of insurance, or increase their insurance premiums.

Third, health outcomes for some individuals may be based on the financial viability of developing drugs. Many drugs and therapies are currently used for large numbers of patients, making them financially viable for pharmaceutical companies to develop. Genetically targeted cancer drugs, suitable for much smaller groups of patients, may be extremely expensive or might not be brought onto the market at all if society is not willing or cannot afford to pay for them.

Fourth, we may be at risk of eroding our quality of life by creating a new state of "worried wellness", waiting for disease to strike.

Finally, we may not be sufficiently savvy consumers. New commercial operators are coming onto the global market offering a range of largely unregulated services. Currently, you don't get much more than details of your ancestry for a US$99 DNA test. But more specialised businesses are emerging that offer, for example, to "identify potential health risks that are present now or may develop in the future".

Is this just hype, and offering unsubstantiated hope to consumers, or does this represent the first stage of patient empowerment over their own health and lifestyle choices? It will be fascinating to watch this new age of personalised medicine develop in the coming years.

DISCLOSURE STATEMENT

The authors do not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and have disclosed no relevant affiliations beyond their academic appointment.

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THE CONVERSATION

Ford, C and Chisholm, O (1 July 2015). *Brace yourself, genetic testing might give you more than you bargained for.* Retrieved from http://theconversation.com on 19 September 2017.

Gene testing for the public: a way to ward off disease, or a useless worry?

If you were destined for dementia in your 60s, but there was nothing you could do about it, would you want to know? David Amor explores the issue

The launch in Australia of a genomic testing service aimed at healthy people heralds a new era of individual patient care. A scan of your genome, which is the complete set of your genes, to find out if you are at risk of particular diseases, can mean you can then go on to take preventive measures against them.

The CEO of the Garvan Institute's Genome.One lab, which is offering the testing, said it would transform the health system, making it more focused on prevention than treatment of disease.

Genomic testing can have tremendous benefits, as in the case of diagnosing children with rare diseases. When applied to the right patients, genomic testing can provide a diagnosis for more than half of patients with unusual symptoms. And the cost of this to the health system is much lower than for traditional diagnostic tests.

Certainly that all sounds like a good thing, but genomic testing is not yet the precision diagnostic and treatment tool we hope it will one day be. And all genetic knowledge is not necessarily helpful. As with any medical intervention, genomic testing carries risks as well as benefits.

Why genomic testing?

Genomic testing takes advantage of recent advances in our knowledge of genetic causes of disease, as well as technology. It's a test of all 23,000 genes in the body at once.

The success of genomic testing in diagnosing rare disorders has raised the question of whether these tests should be performed in healthy people before they become sick. The potential benefits of testing healthy people are obvious, especially when it comes to conditions that have a proven treatment or prevention.

Cancer is a good example of where genomic testing can save lives. A person found to carry a genetic predisposition to bowel cancer can choose to have regular colonoscopies, which can detect and remove pre-cancerous growths before they cause harm.

And because genetic disorders run in families, potential health benefits can extend to other family members who may have the same genetic predisposition.

The ultimate goal of genomic testing, as part of personalised medicine, is that it will be available to everyone, allowing each person's health care to be tailored to their individual genetic make-up. In the future, this "lifetime health resource" promises to improve health care from conception to death.

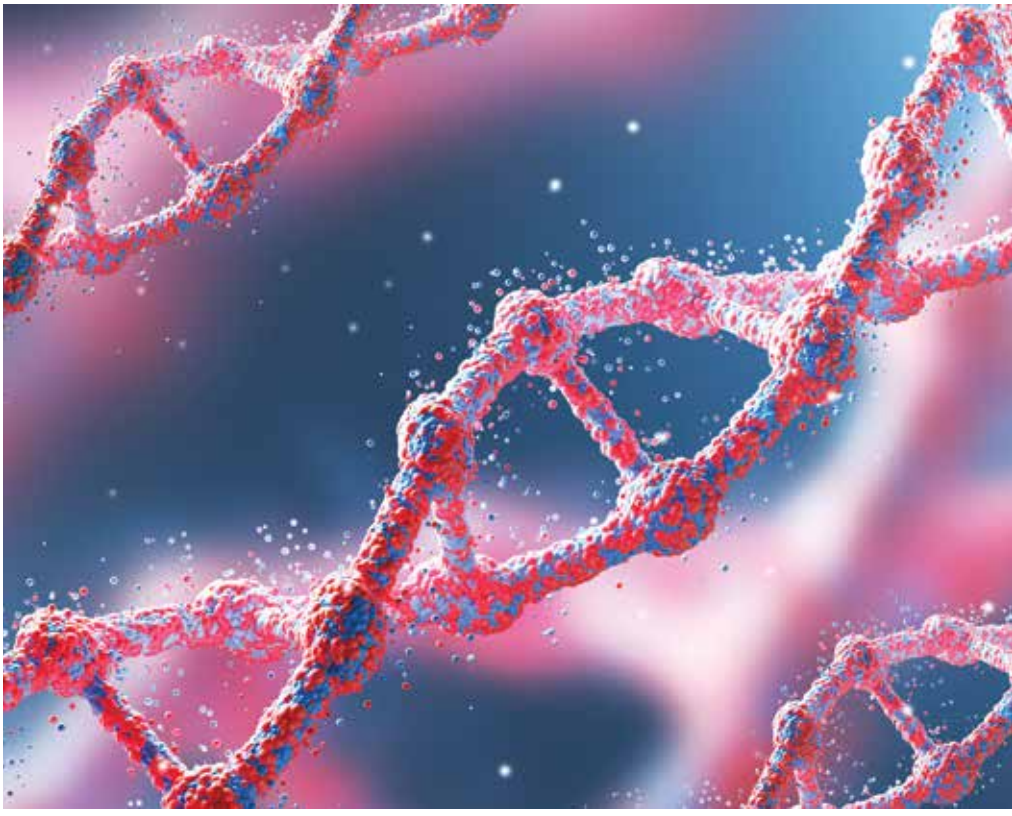
Are we ready for this?

A considerable challenge of genomic testing is the extraordinary complexity of each person's genome. To try to interpret a single human genome is to grapple with literally millions of genetic variants, or points where the person's genetic code differs from the average person's.

Perhaps a handful of these variants will cause disease, but the rest will most likely be harmless. Determining which is which is far from straightforward.

Another problem is that even when specific genetic variants are judged to be harmful, the benefits of knowing this information are not always as clear cut as in the case of bowel cancer. It is an unfortunate

> Even when treatments are available, the benefits of knowing you have a certain genetic predisposition may not outweigh the disadvantages.



While it is hard to argue against a test that just might save your life, currently there is insufficient evidence that the benefits of genomic testing outweigh the risks.

reality that most disorders detectable by genomic testing have no proven treatment or means of prevention.

For instance, particular gene variants may put you at risk of developing dementia in your 60s. But if there was nothing you could do to prevent it, would you want to know?

Even when treatments are available, the benefits of knowing you have a certain genetic predisposition may not outweigh the disadvantages. Consider that genomic testing finds you carry a predisposition to sudden heart death, such as Long QT syndrome. This is an outcome you would certainly wish to avoid. But what if knowing this information caused you to worry more, and the treatment required you to give up sport and take a medication that caused you to feel lethargic every day?

And what if, in the absence of symptoms, your risk of actually dying was only slightly increased compared to the general population? Would you still want to know this information, or perhaps prefer to remain ignorant?

Should we get the test?

The Genome.One clinic at the Garvan Institute in Sydney has addressed some of these concerns by taking a cautious approach. Genetic counselling is provided before and after testing, and although the whole genome is sequenced, analysis and reporting is limited to just 1% of all genes. Most of these selected genes are associated with heart conditions and cancers, and have been chosen because these diseases are well understood, with treatment strategies available.

Genes that cause untreatable diseases, such as dementia, have deliberately been excluded from analysis. This strategy minimises the risk of harm that may come from the test, but the trade-off is that the likelihood of actually finding something useful is greatly diminished. In fact, Genome.One reportedly estimates only 5-10% of people tested will receive an abnormal result; that is, one that will show them to be at risk of disease.

While it is hard to argue against a test that just might save your life, currently there is insufficient evidence that the benefits of genomic testing outweigh the risks. Even for those who can afford the price tag of A$6,400, there are probably more effective targets for our health-related spending. Like many years of gym membership, for example.

DISCLOSURE STATEMENT

David Amor receives funding from the NHMRC and is an employee of the Murdoch Children's Research Institute, which provides clinical genomic testing through its subsidiary, VCGS.

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THE CONVERSATION

Amor, D (22 June 2017). *Gene testing for the public: a way to ward off disease, or a useless worry?* Retrieved from http://theconversation.com on 19 September 2017.

GENETIC DISCRIMINATION

Discrimination against an individual can appear in many forms. As DNA testing increasingly identifies differences in the genetic make-up of individuals, it becomes possible that people will be discriminated against based on genetic information, according to this fact sheet from the National Health and Medical Research Council

What is meant by the term 'genetic discrimination'?

Genetic discrimination describes the different treatment of individuals or their relatives based on their actual or assumed genetic make-up. A person's genetic make-up may be identified by DNA testing or it can be assumed from the medical history of the person's family.

How is genetic discrimination applied in law?

The term genetic discrimination is generally used when people perceive they are being treated unjustly or unfairly because of their assumed or actual genetic status. However, not all behaviour that is perceived as unfair or unjust is necessarily unlawful.

In Australia, discrimination on the ground of genetic status is dealt with in existing Commonwealth, state and territory anti-discrimination laws. These laws generally cover circumstances where discrimination occurs in a public domain such as employment, life insurance, education or access to other services.

What is happening overseas?

If the full benefits of genetic and genomic information are to be realised, the risk of genetic discrimination must be minimised. As a consequence, a number of international statements have called for governments to take steps to prohibit genetic discrimination.

In the US, the *Genetic Information Nondiscrimination Act* was introduced in 2008.

European countries that have introduced legislation to prohibit genetic discrimination include Belgium, Norway, Austria, Denmark, France, Lithuania, Portugal, Sweden and Germany. Other countries, such as the UK, have introduced a moratorium on the use of genetic test information for the purposes of life insurance applications.

Could my genetic information affect my health or life insurance?

The issue of genetic information affecting health insurance does not arise in Australia, as health insurance is 'community rated'. This means that everyone pays the same premium regardless of their personal or family health history or genetic test results, a situation similar to the UK and Canada.

On the other hand, in Australia, genetic information can be taken into account in applications for life insurance products such as cover for death or income protection because these types of insurance are 'risk rated'. However, any risks calculated by insurers to determine premium costs are required to be justified and reasonable.

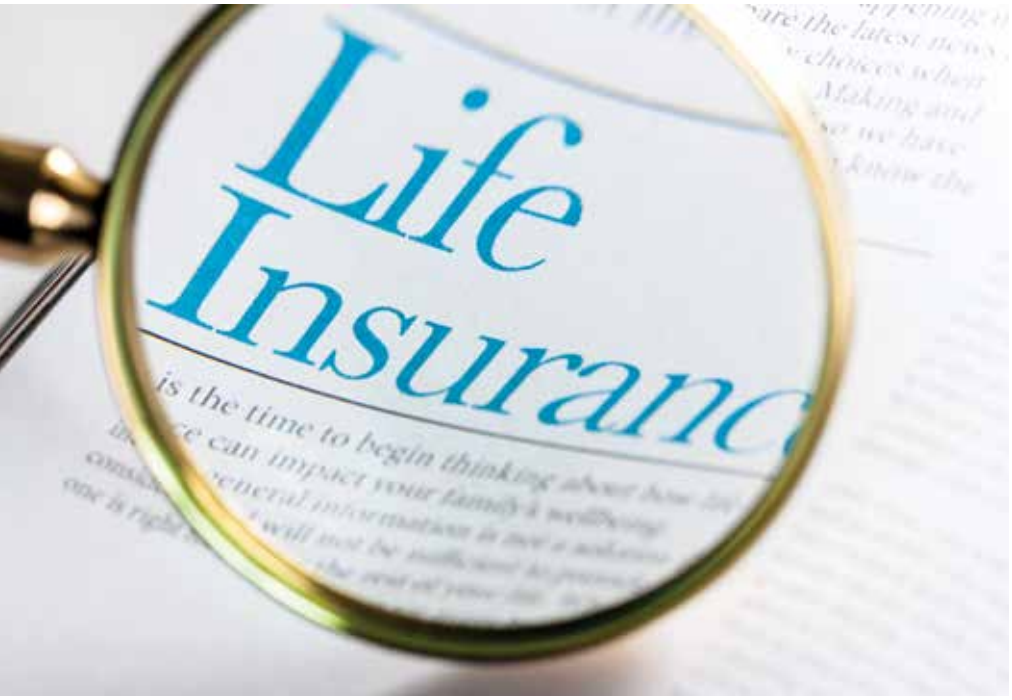
In Australia, the life insurance industry has agreed that it will not require people to have DNA tests before taking out life insurance. However, if individuals have had DNA tests, they must report the results in their life insurance application.

DNA results from research projects only have to be declared to insurers if the participant in the project is informed about their individual results.

National Health and Medical Research Council (December 2013). *Genetic discrimination.* Retrieved from www.nhmrc.gov.au on 22 February 2018.

Australians can be denied life insurance

BASED ON GENETIC TEST RESULTS, AND THERE IS LITTLE PROTECTION



Australia has a lack of regulation to prevent discrimination by life insurance companies based on genetic test results, according to Jane Tiller and Paul Lacaze

A parliamentary inquiry is currently underway into Australia's life insurance industry, which has raised several issues including discrimination by insurers against people with mental health problems. In our submission to the inquiry, we argue comparable discrimination is possible based on genetics, with insurers denying applicants life insurance and raising premiums inappropriately based on genetic test results.

There is a concerning lack of regulation over the use of genetic information by the Australian life insurance industry. Insurance companies are allowed to use genetic test results to discriminate against applicants for life, permanent disability, and income protection insurance (which all come under the life-insurance product category), with little independent oversight or consumer transparency.

This discrimination can deter people from getting genetic tests and being involved in medical research that could prove useful for their future health and scientific understanding of diseases.

GENETIC DISCRIMINATION

Australian insurers can increase premiums, exclude insurance cover for certain conditions such as cancer, or refuse insurance cover altogether purely based on your genetic test results.

Australian insurers can increase premiums, exclude insurance cover for certain conditions such as cancer, or refuse insurance cover altogether purely based on your genetic test results.

Genetic tests look at DNA, the material that contains the instructions for our bodies to grow, develop and function. Some DNA changes cause diseases such as cystic fibrosis or Huntington's Disease, while others can make us more susceptible to conditions such as cancer. Doctors can refer patients to a genetics service if they consider such tests might be of value due to family or personal history.

Although cases of genetic discrimination are difficult to identify, they have been documented in Australia. In one case, a woman with a BRCA gene, which is known to increase breast cancer risk, elected to have both breasts removed to reduce her risk. However, the consequent, significant risk reduction wasn't taken into account by the insurer. When she applied for death and critical illness cover, the insurer excluded any cancer cover and imposed a 50% premium loading for death cover.

In another case, a man whose mother had bowel cancer was found to carry a gene increasing his risk of also developing bowel cancer. He was refused cancer cover despite proactively seeking increased surveillance through colonoscopies, which reduced his risk back down to population average. The man eventually obtained cover, but only after taking a complaint to the Human Rights Commission.

LACK OF REGULATION

Under Australian law, life insurance applicants must disclose any known genetic test results if requested by the insurer. This includes results from approved clinical genetic tests, but also less reliable findings from research or direct-to-consumer (DTC) genetic tests, if they are known to the applicant.

Direct-to-consumer genetic tests are a new concept whereby consumers have genes tested directly through a private company without medical consultation. Although most of these lack evidence of any predictive medical value, the law does not distinguish between types of genetic tests.

Australian life insurance companies are technically required by law to justify decisions based on genetic results. In practice, however, consumers have no way of requiring insurers to provide information

about how decisions are made.

The Australian government leaves the life insurance industry to self-regulate its policy through the Financial Services Council (FSC). This essentially means the insurance industry writes its own rules on the use of genetic data, raising obvious conflicts of interest. Recently the FSC updated its genetic testing policy to suggest that insurance companies ask applicants if they are considering having a genetic test. This is a concerning development.

Many other countries have protected consumers by restricting or banning the use of genetic information for insurance altogether. In the UK, a moratorium established in 2001 sets out an agreement between the government and the insurance industry not to ask for, or use, genetic test results (except for Huntington's Disease for policies worth over £500,000).

Canada has just passed legislation prohibiting insurance companies from asking for any genetic test results. And many European countries such as Belgium, Austria, Denmark, France, Germany, Lithuania, Norway, Portugal, and Sweden have implemented outright bans or other regulation in accordance with the Council of Europe's *Oviedo (human rights and biomedicine) Convention*.

IMPLICATIONS

In Australia, the situation is very different. Patients considering predictive or family-based clinical genetic testing are frequently advised to review their life insurance situation prior to taking the test, due to the obligation to disclose results to insurers.

As genetic testing becomes more widespread in our society and offers increased potential to help manage patient risk, we must find a way of regulating the insurance implications.

The fear of unknown insurance implications deters some of these people from having this testing. This can sometimes mean passing up critical information that can be used to help prevent cancers and other serious diseases.

For example, one study looked at patients at risk of bowel cancer due to family history. It found more than double the patients, who had been advised of the possible effect of having a positive test on their insurance claim, declined testing compared with patients who had not been advised of this possible effect.

Some participants are also being deterred from involvement in medical research, which can sometimes involve the return of genetic findings. Fortunately, this issue only affects life insurance and related policies in Australia, not private health insurance, which is treated differently. However, this distinction isn't always understood by consumers, who may mistakenly believe that these issues affect all insurance types.

As genetic testing becomes more widespread in our society and offers increased potential to help manage patient risk, we must find a way of regulating the insurance implications.

The Australian government must take action towards an immediate ban (moratorium) on the use of genetic test results in insurance, until adequate long-term regulation is in place. This would bring us in line with other countries.

DISCLOSURE STATEMENT

Paul Lacaze receives funding from NHMRC and NIH. Jane Tiller does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond her academic appointment.

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THE CONVERSATION

Tiller, J and Lacaze, P (25 August 2017). *Australians can be denied life insurance based on genetic test results, and there is little protection.* Retrieved from http://theconversation.com on 19 September 2017.

CHAPTER 2

Gene ethics: risks and benefits

ETHICAL ISSUES IN HUMAN GENETICS AND GENOMICS

This fact sheet from the Centre for Genetics Education describes some of the ethical issues that can arise because of the use of genetic testing

In summary

- The nature of the information gained from a genetic test raises addition ethical issues compared to other health information.
- Genetic testing is best offered by specialised services such as a clinical genetics service.
- Laboratories undertaking the testing should be accredited.

WHY IS GENETIC INFORMATION SPECIAL?

Genetic information is often considered exceptional when compared to other medical information about an individual for a number of reasons.

Shared nature and ownership of genetic information

Genetic conditions are family health problems. A diagnosis or a finding of inherited predisposition in a family member has implications for other family members.

Health professionals have an ethical responsibility to prevent harm or avoid seriously jeopardising the health of others (the duty of care). Similarly, individuals undergoing genetic testing have a responsibility to consider not only what it means for their own health, but also what the information may mean for their relatives, and their responsibilities towards those relatives.

Geographic distance or discord in families can sometimes lead to difficulties in revealing genetic test results that may be important for other family members.

Responsibility and obligation however needs to be balanced with the right of an individual to choose to know their personal genetic information or, equally, not to know.

The emphasis needs to be on the right of the person to choose. Genetic counselling is essential both before and after genetic testing so that all the implications of undertaking testing including having information which might be of interest to others can be understood.

Limitations of genetic testing

While in some cases, genetic tests provide reliable and accurate information on which people can make decisions, in other cases it may not be possible to obtain a definitive result.

An individual is much more than the sum of their genes: the individual's environment can modify the expression of genetic messages to the body and many health factors are not genetic.

The discovery of a variation in a particular gene may provide some information about the nature of the condition that the person has, will develop or for which they may be at increased risk, but can rarely predict the severity of the condition or the age at which symptoms will first onset.

This lack of precision in relating the expression of the condition (called the **phenotype**) to an individual's genetic make-up (called the **genotype**) can make the decision-making process in regard to acting on the information very challenging.

This is particularly so when the genetic testing is done for prenatal testing of a condition. Genetic counselling is essential to assist families in that decision making process and ensure that the decision is as informed as possible.

Predictive/pre-symptomatic testing – generally for adult-onset conditions

This type of genetic testing applies to families in which an underlying genetic cause for their condition has been identified and can be used to identify currently healthy family members that are at-risk, if they wish to do so.

Pre-test counselling is important in these cases and aims to provide accurate information so that the individual can make an informed decision about whether or not to have testing.

This is called **informed consent** and means that the person undergoing the test should only do so on a voluntary basis and with a full understanding of all the implications. There can be a danger of coercion, for example, an enthusiastic researcher or a member of a family may try to persuade others in the family to undergo testing about which they feel uncomfortable.

Discussion of the potential **emotional impact** on **family members** of finding out test results should also be undertaken before testing. This can be substantial whether the results are bad or good, for example the feelings of guilt often felt by 'survivors' who have not inherited the gene fault.

When a problem with a developing baby is detected, support is essential for whatever difficult decision is made.

Discussion of implications for other family members and obligations to inform, as well as the potential interest of third parties in genetic information revealed by testing such as insurance and employment, are also important.

The potential for discrimination

Genetic testing may impact an individual's ability to obtain life insurance and employment in certain professions. This is especially the case with predictive/presymptomatic testing which provide information about an individual's future health.

Reproductive choices/prenatal testing

Whether or not to have children is a major decision for any individual. It is even more difficult where one or both of the prospective parents knows or suspects that they may carry a faulty gene associated with a health problem which could affect their children.

The decision to have a baby may lead to a number of further decisions to be made in regards to the possible genetic testing of the embryo/fetus during the pregnancy. Limitations of such testing are the same as those discussed previously, in particular detection of a faulty gene or a chromosomal change may not provide all the information about the potential or quality of life for the child or the severity of a particular condition.

When a problem with a developing baby is detected, support is essential for whatever difficult decision is made.

Some expectant parents will decide to continue the pregnancy and try to put in place the professional, medical and social support that will be required. Others may choose to terminate the pregnancy. This decision may conflict with moral, religious and cultural beliefs.

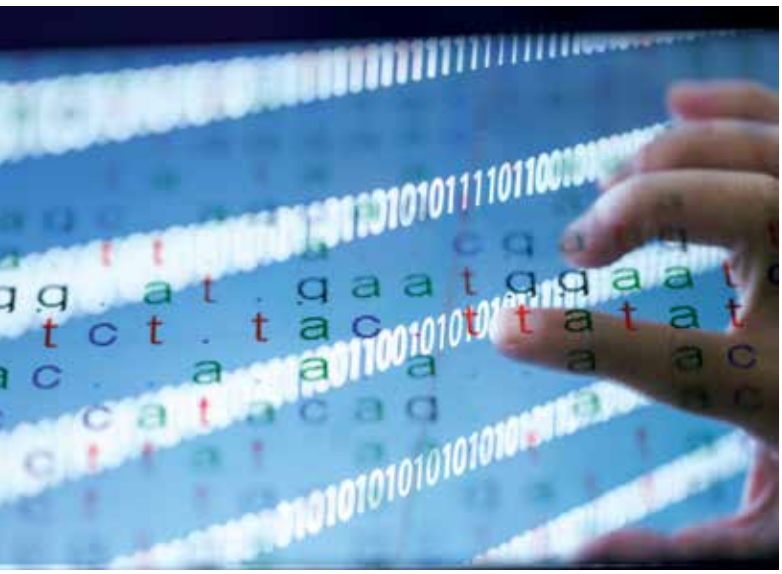
Different individuals, communities, cultures and religions have different perceptions of disability and this may raise additional issues.

Inappropriate applications of genetic testing

Genetic testing has many potential applications, however some of these are in conflict with what we could consider ethical. These include use of genetic testing to confirm paternity sex selection of a fetus for family balancing reasons without the informed consent of all parties involved.

Setting boundaries in applications of the genetics technology

Philosophers on science have put the view that science is morally neutral. It is the uses to which the science is put that might be good or bad. With the new advances



To know or not to know? When is the right time to decide to have predictive/ presymptomatic testing?

in genetics, as with any powerful new scientific tool, there is a potential for abuse. Controversial applications of genetic testing such as reproductive cloning and genetic testing for enhancement create a huge challenge worldwide and require implementation of international regulations on the boundaries within which these applications can be applied.

Moral, religious and cultural beliefs underpin decision making by individuals, couples, families and communities and may challenge such boundaries.

CASE STUDY

Huntington disease (HD) is a neurological degenerative disease that has an onset in most people between the ages of 30 and 50. There is no cure for this condition and it is progressive. Symptoms include deterioration in movement, cognition and generalised functioning. Death usually results from respiratory illness.

HD is an inherited condition. A child of an affected person has a 50% chance of inheriting the faulty gene that causes the condition. Genetic predictive testing is now available for persons over the age of 18 who have an affected parent or relative which will tell them in almost all cases whether they will develop the disease at some stage in their life.

Worldwide, of those eligible for the test, only around 15% of people have taken up the option of testing.

Mr H is a 25 year old man whose grandfather died some 10 years ago from Huntington disease. Mr H's mother has therefore a 50% chance of developing HD. She decided to have the genetic test and has been shown to have the faulty gene. She will definitely develop HD at some time and Mr H is now at 50% chance of developing HD.

Mr H is an air traffic controller. He loves his job and he feels he could perform his duties most adequately for many years, irrespective of whether he carries the faulty gene for HD or not. He does not wish to have the genetic test. His employer is unaware of his family history.

DILEMMAS

- To know or not to know? When is the right time to decide to have predictive/presymptomatic testing?
- Do employers in industries involving public safety have the right to demand family health history information? In cases where genetic predictive testing is available for conditions that may impact on public safety, do employers have a right to predictive testing information about an individual whose current health status is excellent?
- Who actually 'owns' this information and who should decide who can access it?
- What if the situation was reversed and Mr H wanted testing but his mother had refused? What responsibility is there to offer testing to an individual when the result may indirectly reveal the genetic status of a relative (if Mr H carries the HD gene fault then he must have inherited from his mother)?
- Implications for Mr H's reproductive choices.

Forensic DNA databanks

The use of fingerprints (more accurately known as dermatoglyphic fingerprints) for forensic identification purposes has been in place since the 1890s. One hundred years later, **DNA fingerprinting** is being used to complement the traditional system, or is being used in isolation for identification. The public has also contributed to investigations of unsolved crimes by volunteering genetic samples. Overall there is a need to ensure that samples are used for the purpose for which they were collected and protected from misuse.

Patenting of genes

The issue of patenting genes as recognition of the intellectual achievement required to isolate a single gene from the 20,000 or so genes in the cell is contentious.

In Australia there have been three inquiries into the issue of gene patenting and human health, including the Australian Law Reform Commission in 2004, the Senate Community Affairs Reference Committee in 2010 and the Advisory Council on Intellectual Property in 2011.

The Federal Government issued a response in 2011 confirming that the government does not support the absolute prohibition of gene patenting, however will aim to ensure that gene patents do not lead to patients being denied 'reasonable access to healthcare'.

Centre for Genetics Education (15 June 2016). *Fact Sheet 19: Ethical Issues in Human Genetics and Genomics.* Retrieved from www.genetics.edu.au on 19 September 2017.

GENE THERAPY

Gene therapy has the potential to revolutionise treatment for all kinds of genetic conditions, according to this fact sheet from Better Health Channel

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.

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.

This type of gene therapy is called 'therapeutic gene therapy' or 'the use of genes as medicine'. It is an experimental form of treatment that is still in its infancy but has the potential to revolutionise treatment for all kinds of genetic diseases.

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.

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.

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.

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.

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.

The current problem is to find a way to successfully 'deliver' the working version of the gene.

- **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, 1,698 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.

Gene therapy offers a range of complex ethical and moral dilemmas ... The concern is that manipulating factors such as intelligence might be tried, once gene therapy becomes commonplace ... Another concern is that gene therapy might only be available to the rich.

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 doctor
- Genetic Health Services Victoria, Royal Children's Hospital Tel. (03) 8341 6200

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GENE EDITING AND CRISPR

CRISPR is a breakthrough tool for genetic technology that opens new frontiers for science and new questions for society, write Roman Dronov and Will Howard in this occasional paper produced by the Office of the Chief Scientist

In 2003, scientists announced that the first human genome sequence had been mapped in full. The map took 13 years and more than US$3 billion in public funds to complete, and was one of the largest global scientific collaborations ever attempted.

By 2016 – just 13 years later – a complete indvidual human genome could be sequenced in a day for US$1,000. With falling costs has come growing availability and a wealth of genetic information in all manner of organisms. We are living in a golden age for biological research.

Against the background of this veritable tsunami of genetic sequence information, the rapid development of a technology known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has opened a bold new chapter. CRISPR is transforming not just how we undertake genetic research, but how we live our lives – from the food we eat, to the industries we develop, to the years of healthy living we enjoy.

This paper explains what CRISPR is, why it is having such an impact on the scientific world, and what it could mean for our future.

GENE TECHNOLOGIES: A TIMELINE

Life has always been exposed to changes in genetic material through natural processes. Random changes (or 'mutations') can be caused by environmental factors or errors in organisms' biological processes. They can occur in all organisms, including humans, and are one of the driving forces of evolution.[1]

With the dawn of agriculture some 12,000 years ago, a new kind of modification began to take off – domestication and selective breeding (Figure 1).

Our ancestors selected and bred the plants and animals most useful to them. Advantageous traits were chosen in the offspring. Over many generations this selective breeding, together with influence from the environment, resulted in significant changes in the genetic information of these species. This process continues in agriculture and ecology today.

With growing understanding of the processes of genetic inheritance and the nature of DNA, scientists began to search for ways to directly target genes encoding specific traits, rather than laboriously breeding organisms to favour desired characteristics.

From the 1970s, this research provided the first products classed as genetically modified organisms (GMOs), most of which were produced by introducing DNA sequences from different species into host organisms.[2]

Gene editing is the next step in precision and control. Where previous methods of gene modification were laborious and expensive, editing technologies allow scientists to pinpoint the exact site in the DNA that they want to alter.

As an analogy, if the text of this paper were equivalent to an organism's genetic information, older gene modification tools could insert new words – copied from another document – randomly anywhere in the sequence. New gene editing techniques can add, delete, or change one letter in the middle of a specific word.

Key messages

- CRISPR provides an unprecedented level of precision and control in gene editing work.
- It is a versatile tool with potential applications in healthcare, agriculture, industry, and environmental management.
- Effective regulation and community engagement are essential to responsibly develop this technology.

Terms to know

DNA (deoxyribonucleic acid) is nature's way of storing genetic information. It can be viewed as a program or recipe book containing instructions on how a particular organism will develop.

A **gene** is a section of DNA that controls a specific trait – for example, hair colour, eye colour, or blood type. In some cases, several genes interact to produce the final result.

Gene editing involves making precise changes to DNA in order to change a gene or the expression of a gene. This can be used to turn some genes 'on' or 'off' (a potential treatment for genetic disorders), or to enhance a particular trait (better crop yields).

ENTER CRISPR

In a fast-developing suite of gene editing technologies, CRISPR stands out for its simplicity, versatility, speed and precision.[3] As a result, CRISPR is a rapidly-growing topic of research (Figure 2).

> *"This is not genetic modification as people have imagined it since the 1980s. This is something fundamentally different: a pair of scissors that we can wield with nuance, efficiency and control.*
>
> Dr Alan Finkel, Australia's Chief Scientist

CRISPR gets its name from a DNA 'library' that acts as an immune system in bacteria. In nature, the library documents snippets of DNA from viruses and other organisms that have attacked the host bacterium in the past – like a wall of criminal mug shots in a police station.

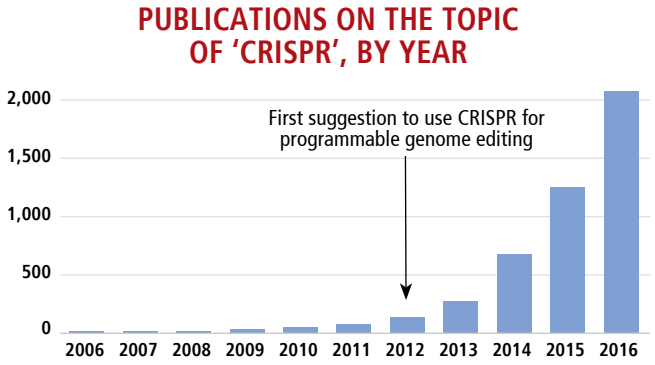

Figure 2: The number of CRISPR publications has rapidly increased in recent years.
Source(s): Web of Science

The 'police' in this situation are CRISPR-associated endonucleases (Cas). These are enzymes that cut up DNA. The Cas enzyme is given a guide sequence or target 'mug shot' from the library. This allows the Cas enzyme to head out, recognise and arrest that specific invader.

By aiming the Cas enzyme at a new target – or providing it with a new mug shot – this system is able to accurately defend against a wide range of attackers.

While CRISPR naturally occurs in bacteria, it can work wherever a Cas enzyme and a guide sequence (mug shot) are introduced.

In the laboratory, researchers can write their own guide sequences and direct the Cas enzyme to cut the cell's DNA at any chosen target location specified by that guide sequence. The editing occurs when the cell repairs the cut DNA. If we supply new DNA then the cell will stitch in the new code. In this way, we can write new words in an organism's genetic code.

Editing genes with CRISPR

A cut made by the Cas enzyme can be repaired in two ways. 'Non-homologous end-joining' is prone to introducing errors: for instance, it may delete a small DNA region during repair, effectively 'knocking out' that gene.[4] Alternatively, DNA containing desired new edits can be added to alter the nature of a gene. Insertions made by this process can incorporate point mutations or deletions in the precise location of the cut, often used intentionally by scientists to turn a particular gene off.[5,6,7]

APPLICATIONS OF CRISPR

Agriculture and the environment

CRISPR techniques could transform the agricultural sector: mushrooms that resist browning and disease-resistant wheat strains are just two examples of what has already been achieved.

Projects to improve yield, reduce waste or improve the health of crops and farm animals are widespread. In September 2016, a researcher from Umeå University in Sweden captured media attention by enjoying a meal including CRISPR-modified plants that he cultivated and grew himself.[8]

As well as increasing the efficiency of agriculture, gene editing could address a range of ecological issues associated with farming. One example is the potential use of CRISPR to knock out reproductive genes in farmed species to make them sterile unless provided with specific chemical signals while in captivity.[9] Any potential escapees could not reproduce in the wild and disrupt ecosystems. This technology could be used to provide an additional safeguard for the farming of animals such as rabbits.

Health and medicine

Gene editing holds great potential to improve human health, particularly in the area of 'precision' medicine.[10]

For example, CRISPR has the capacity to redefine gene therapy for treating cancer, allowing reprogramming of a person's own immune cells to recognise and attack malignant tumours.[11]

We can expect CRISPR to contribute to the development of 'farmaceuticals' – medicines produced through existing animal farming practices.[9] Prior to CRISPR, in 2006 the European Union and in 2009 the US Food and Drug Administration approved a breed of goat that produces an anti-clotting protein in its milk. In 2015, both agencies approved a genetically-modified chicken breed that expresses an anti-cholesterol drug in its eggs. Now, through CRISPR, CSIRO scientists are developing chickens that produce hypoallergenic eggs.[9]

The first clinical trial involving the injection of cells containing CRISPR-edited genes into a human patient is already underway in China. This trial is using CRISPR-edited cells to treat an aggressive form of lung cancer.[12]

New trials are also anticipated to begin in the US in 2017, with an advisory committee of the US National Institutes of Health approving a proposal to remove, edit and re-infuse T cells (human immune system cells that can destroy tumour cells) from patients with several types of cancer.[13]

CRISPR also opens the door to editing genes that cause serious illness in humans. These changes would be limited to particular individuals when performed on somatic (non-heritable) cells, such as immune or lung cells.

Figure 1: The teosinte plant (left) has been selectively bred over millenia to yield sweetcorn (right) – a much larger and sweeter vegetable.

CRISPR IN AUSTRALIA

Australia has emerged as an important player in the gene editing age, building on its traditional strengths in the life sciences and commercialisation of biotechnology research. It is currently the sixth most prolific producer of CRISPR publications worldwide per capita.

Combined with a strong record of responsible regulation, robust intellectual property framework, and a highly regarded clinical trials sector, the potential for future investment and discovery could be substantial.

Australia is developing applications of gene editing to solve issues for agricultural industries, such as sex determination for egg production. CRISPR will also have impacts in generating new biotechnology industries.

In the context of the Australian environment, gene editing holds particular promise in helping to deal with invasive species and biocontrol measures. Programs are underway using CRISPR editing to develop mitigation strategies for cane toad invasion, whilst daughterless technology is under development at CSIRO to safely control carp by removing females from populations.

Gene drives could also play a key role in eradication of mosquito-borne diseases, such as dengue fever, Ross River virus and Murray Valley encephalitis.

Caution must be exercised, however, before conducting modification of germline (reproductive) cells that would allow changes inheritable by future generations.[14] This potential application raises serious ethical concerns, with a recent report by the US National Academies of Science, Engineering and Medicine offering advice on the science, ethics and governance of human genome editing.[15]

NEW RESEARCH FRONTIERS

CRISPR could potentially prevent the spread of vector-borne diseases, such as dengue fever or malaria, by modifying mosquito populations through the use of 'gene drives' – an emerging system that allows rapid propagation of introduced genes through a large population.[16] Based on studies conducted on mosquitoes, yeast, and fruit flies, these introduced genes have on average about a 95 per cent probability of propagation through each generation[17] – far greater than the 50 per cent probability common in nature.

These gene drives could be used to either rapidly reduce the populations of specific types of mosquitoes known to carry target diseases, or to make populations of mosquitoes less likely to transmit diseases. However, the effects of gene drives altering or eliminating entire populations requires careful environmental and ethical consideration before implementation.[18,19]

Researchers have also proposed using CRISPR to bring extinct species back to life. Potential targets of de-extinction include the woolly mammoth, passenger pigeons, dodo birds, and the thylacine (Tasmanian tiger).[20,21,22] While the feasibility of such proposals is unknown, they prompt us to ponder the implications of such life-altering interventions.

PROCEEDING RESPONSIBLY

The rapid uptake and increasing sophistication of gene editing tools presents a series of highly complex economic, social, legal and ethical questions. Different countries have attempted to resolve these questions in different ways, with progress in science sometimes outpacing the capacity of governments to legislate for appropriate regulatory coverage of rapidly-developing technologies.[19]

The regulatory frameworks developed to regulate older gene modification techniques are constantly being updated for new technologies. Despite this, delays may deter investment and frustrate researchers seeking to develop the technology in line with community aspirations and values. On the other hand, caution demands that a high level of attention is paid to safety, efficacy and utility before the introduction of a new technology.

In Australia, the Gene Technology Regulator is the statutory office holder regulating dealings with GMOs, including organisms with genes inserted using CRISPR techniques (e.g. engineered gene drives). They assess all licence applications for work with GMOs, and contribute substantially to Australia's strong record of responsible and effective regulation of biotechnology research and commercialisation. Products produced from GMOs – such as food from a genetically modified (GM) crop – are regulated by other bodies. Food Standards Australia New Zealand (FSANZ), for example, is responsible for the safety assessment and approval of GM foods before they can be sold for human consumption in Australia or New Zealand.

In 2012 and 2013, FSANZ convened workshops that concluded that food derived from gene edited crops with small changes – such as those produced using CRISPR techniques – need not be considered GM because such mutations are indistinguishable from mutations that might occur naturally or through traditional mutagenic techniques. However, it was concluded that foods from edited crops with inserted genes should be categorised as GM. FSANZ is currently reviewing the definitions of GM food to consider whether food derived from new techniques, including gene editing, should be subject to assessment and approval as GM foods.

Australia's strong regulatory environment will be key to applying, monitoring and commercialising these techniques, particularly as these techniques become more available outside the traditional academic laboratory.

At the time of writing, the Gene Technology Regulator is undertaking a technical review of the Gene Technology Regulations 2001 to provide clarity about whether organisms developed using a range of new technologies, including CRISPR techniques to make small changes, are subject to regulation as GMOs. The review also aims to ensure that new technologies are regulated in a manner commensurate with the risks they pose to human health and safety and to the environment.

Conclusions

While the potential of gene editing is vast, the use of these powerful tools has only just begun. It is up to governments, scientists and the community to work together to decide what outcomes we want, what risks we are prepared to manage, and how the benefits will ultimately be shared.

About this series

These occasional papers from the Office of the Chief Scientist aim to highlight scientific issues of importance to Australian society. Each issue has been prepared by a multi-disciplinary team and has been through an external review process.

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Dr Roman Dronov and Dr Will Howard are from the Office of the Chief Scientist.

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Human embryo CRISPR advances science but let's focus on ethics, not world firsts

JUST BECAUSE WE CAN EDIT GENES IN HUMAN EMBRYOS, DOES THAT MEAN WE SHOULD? HANNAH BROWN INVESTIGATES

Following early reports last week that scientists had edited the DNA of human embryos, American researchers have now published their much anticipated paper in the journal *Nature*.

The human embryos used in the research were created using eggs collected from healthy women and sperm from a man carrying a DNA error. Thus some of the embryos carried the DNA error, and some were "healthy".

Led by Hong Ma of Oregon Health and Science University, the researchers then used the gene-editing technology known as CRISPR in the embryos to try to correct the error, which causes catastrophic genetic heart disease in adults.

In more than half of the embryos, the DNA mutation was replaced with "healthy" DNA, and these embryos appeared to grow normally to the blastocyst stage (the point at which they would normally be transferred back into the woman's uterus during the IVF process – in this study, the blastocysts were destroyed during analysis).

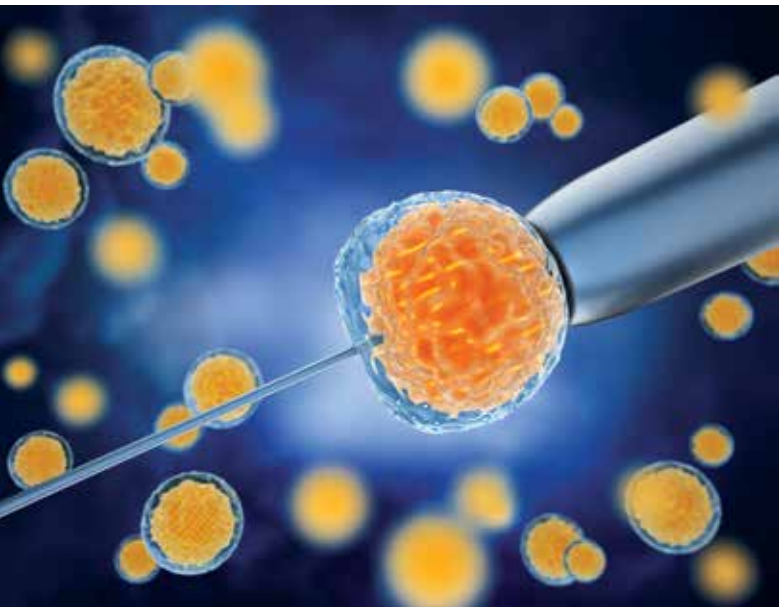
Simply put, CRISPR is like a sat-nav-guided pair of molecular scissors. It is directed to a specific location in the DNA and performs a cut-and-paste function, not unlike word-processing software.

Genetic diseases are a significant cause of healthcare spending and death globally, and many research groups are using CRISPR as a tool to try to combat them.

This latest paper is not the first time human embryos have been genetically modified, and is one of many examples of CRISPR being successfully applied to remove a target gene.

But it is the first time a disease-causing mutation has been repaired in a significant number of healthy human embryos, created specifically for research. And, for me, this advance is both notable and problematic all at once. It creates a leap forward in several key aspects of science. On the other hand, it highlights ethical dilemmas that we regularly grapple with in reproductive health.

So many questions remain. When and how will we know that it is time to create a living, breathing human from a modified embryo? Should we take the risk of proceeding with the first full-term human pregnancy, not knowing if the technology will have unexpected adverse consequences?



Science win: we know more about embryos

From a purely research perspective, this paper is an exciting advance.

CRISPR gives us the ability to edit embryos one gene at a time, to learn about the events that happen in the first five days of life, and to tease apart how the sperm and egg come together to form a ball of cells, which ultimately go on to form a healthy baby.

It may also help us to understand more about infertility, miscarriage and stillbirth, plus many diseases and disorders, by making better and new animal models of disease.

Science win: the right timing improves CRISPR

Building on previous research from other groups, in the new research Ma and colleagues improved the success rates of DNA editing by changing the timing.

By using CRISPR to alter the DNA just as the sperm and egg came together, they improved the frequency at which the editing happened, and also how often it was correct. The issue of timing presented challenges in previous attempts, where mistakes were frequent.

There is still room for improvement though, with small mistakes still incorporated, meaning these embryos would never be suitable to transfer to a patient. We are by no means at the point where this technology is ready for use.

Ethical quandary: editing healthy embryos

Unlike research groups before them – which worked on embryos that were not capable of ever becoming a baby – this study involved the creation of healthy human embryos specifically for research purposes.

Scientific research is sometimes faced with these

Catch-22 moments where advancement is not likely without facing enormous moral and ethical challenges. Some of science's greatest breakthroughs have used animal models or questionable experiments on humans.

As detailed in the paper's research methods, the scientists adhered to strict ethical guidelines, and were monitored closely by committees of individuals including not just scientists and doctors, but also members of the general public.

Research using human embryos is highly regulated, and is different between countries. In Australia, the National Health and Medical Research Council has a strict set of guidelines, meaning that all research performed on human embryos is monitored very closely, and many limitations exist.

Ethical quandary: multiple opinions matter

Science is not as simple as just being able to perform a biological technique successfully in a laboratory setting. Research must proceed only with extreme caution.

Concurrent with advances in benchtop biology, multidisciplinary teams of biologists, IVF specialists, psychologists, bioethicists, social scientists, policy makers and advisers, disability advocates, and most importantly consumers (as well as many others) must work together.

If one day scientists are positioned to perform genome editing safely in humans, this should only happen if society considers it useful, appropriate and desirable.

Ethical quandary: where to from here?

As a biologist, understanding if this technology is safe, and whether a healthy human baby can be born from a genetically modified human embryo seems unanswerable right now.

So many questions remain. When and how will we know that it is time to create a living, breathing human from a modified embryo? Should we take the risk of proceeding with the first full-term human pregnancy, not knowing if the technology will have unexpected adverse consequences?

Seeing more experiments being performed in larger animal models (agricultural species like cow and pig) and in non-human primates will be essential. This step should – in my opinion – be a research priority, before more healthy human embryos are used for research purposes.

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Hannah Brown is Post-doctoral Fellow; Reproductive Epigenetics, University of Adelaide.

THE CONVERSATION

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Human genome editing report strikes the right balance between risks and benefits

GENE THERAPY IS GROWING IN ITS CAPABILITIES, BUT THERE SHOULD BE LIMITS TO ITS USE, NOTES MERLIN CROSSLEY

If you recognise the words "CRISPR-mediated gene editing", then you'll know that our ability to alter DNA has recently become much more efficient, faster and cheaper.

This has inevitably led to serious discussions about gene therapy, which is the direct modification of someone's DNA to rectify a genetic disorder, such as sickle cell anaemia or haemophilia. And you may also have heard of deliberate genetic enhancement, to realise a healthy person's dreams of improving their genome.

Both of these issues have now been tackled in a comprehensive report on gene editing released today by the US National Academy of Science and National Academy of Medicine.

The message is fairly simple: relax, we've seen this all before, little if any harm has eventuated, and society is well placed to move forward together on this.

A DEFINITE MAYBE

Of all human technologies, recombinant DNA has arguably been one of the safest. There have been multiple benefits in both medicine and agriculture. And the legitimate concerns that arose when viruses were first mixed with bacterial genes, when cloning was first introduced, and when stem cells were developed, have not come to pass.

I cannot list all the benefits here, but if you have received the Hepatitis B vaccine or Australian Ian Fraser's Gardasil vaccine, which protects against cervical cancer viruses, you have been protected from disease thanks to recombinant DNA technology.

However, you probably haven't received somatic gene therapy, which is gene alteration directed at fixing one cell type, such as defective blood or liver cells. This is because this therapy only touches a tiny number of people, probably fewer than 1,000 worldwide, and again the benefits have outweighed the risks.

But there is one new message in the report that will grab the headlines. That is the view on human germline gene therapy, which entails modifications that would be passed on to children and then to their children. This kind of gene therapy has been considered highly controversial. But this time, instead of a simple *no thanks* there's a *definite maybe*, provided the therapy is targeted at a severe disease as a last resort.

There will be alarm in some circles at the very mention of germline gene therapy, although perhaps not from the very few people who might be contemplating such treatment for the sake of their future children.

There will be alarm in some circles at the very mention of germline gene therapy, although perhaps not from the very few people who might be contemplating such treatment for the sake of their future children.

The authors of the report, who are among the mostly highly respected experts in the world, are well aware that many people will not be comfortable with the thought of germline gene therapy. They stress the need for extensive consultation, the meeting of strict criteria, and close regulation.

But in weighing up safety and efficacy, social and individual benefit, they clearly don't want to see a reflex ban put in place that may limit options if this technology can be used to make the life of some individuals better.

On one hand, they are right. This technology is not a threat to the fabric of society. Nor, I'd say, is this a genie that could not be put back in the bottle; gene editing could be reversed.

Nor, like the *Sorcerer's Apprentice's* broomsticks, will it multiply and spread when we try to restrain it. This is not like letting slip a virus, cane toads, oozing radioactive waste or carbon emissions into the atmosphere.

Seeking germline gene therapy in order to have a disease-free child would be a choice made at a personal level and those not wishing to participate should never feel compelled to do so.

Except, of course, the children who would not have a say in it. But also for them the risks might well outweigh the benefits. And, one way or another, parents already make life-determining choices for their children and sometimes for their children's children.

Even those seeking germline therapy for the sake of their children would mostly have alternatives, such as preimplantation diagnosis, which itself also has ethical considerations. There are no easy answers here.

So I can understand the report's conclusion, although I also believe there are risks, which I'll mention below.

HARD TO ABUSE

There are other aspects of the report worth mentioning. It confirms that we already do properly regulate laboratory-based gene modifications, and we have learned so much from previous somatic gene therapy efforts that we are well placed to push on safely with both research and somatic treatments. I agree with this.

It also says that actual genetic enhancements should be avoided. There is evidence that society is uncomfortable with the idea of individuals, who are not suffering

from disease, improving either themselves through somatic therapy or their bloodlines through germline genetic enhancement.

Some people might want more copies of the p53 tumour suppressing gene or to lose their CCR5 gene, which helps HIV invade cells, in order to give their children possible protection from cancer or HIV respectively, but I'd have to say it isn't worth the risk.

I would add that, ethical reservations aside, the sheer complexity of our genomes, and the rather involved and lengthy process of human reproduction, means that I have no concerns that even the craziest world leader could ever generate an army of super-mutants. Such an ambition would be defeated by not knowing which genes to alter, not to mention the requirement to assemble tens of thousands of surrogate mothers, then wait 20 years for the army to mature.

Yes, it is possible that someone somewhere will attempt germline gene enhancement as a stunt. That would be wrong and dangerous, and a risk for the child. But it would not threaten society any more deeply than many other obscene and regrettable individual crimes that sadly occur every day.

Germline gene therapy is illegal in many countries, and although there is a risk that unfortunate "medical tourism" may occur at some stage, I don't expect this to be a greater problem than the already widespread snake-oil selling that is a feature of many economies.

Even those seeking germline therapy for the sake of their children would mostly have alternatives, such as preimplantation diagnosis, which itself also has ethical considerations. There are no easy answers here.

NO EMERGENCY

So am I comfortable with this report and confident that it covers the ethical issues? I think it is superbly written. It is accurate, up to date, balanced, thoughtful, and covers experiments, somatic therapy, germline therapy, genetic enhancement, societal responses, and the need for public consultation and careful regulation. There is no emergency here.

My main concern is that raising the prospect of germline gene therapy will trigger discussions that will divert us from more pressing issues.

I do worry that introducing this apex concept as a possibility may increase the number of people who fixate on what gene therapy could deliver and thus may be lured into medical tourism, both desperate patients and also foolish investors, and all the while charlatans will profit from peddling promise.

I worry that raising hopes too high too quickly will ultimately cause a backlash against more moderate science.

I also worry that even conventional funding bodies will succumb to understandable pressures to fund translational research prematurely and this will actually waste large amounts of valuable public money.

And I worry about a hysterical reaction that could divide society along political lines with people lining up for or against germline gene therapy based on their political positions or personal beliefs rather than a sober examination of the facts, risks and contexts.

Finally, I worry that the focus on human modification will distract us from other issues, such as the use of CRISPR-mediated gene drives that could be used to eradicate rapidly reproducing organisms such as mosquitoes, and could thus be used for both great good or great harm.

But I don't feel the burden of worry too much because I know that, as a scientist, I can and should share the weight of my concerns with society.

DISCLOSURE STATEMENT

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EXTREME GENETIC ENGINEERING AND THE HUMAN FUTURE

RECLAIMING EMERGING BIOTECHNOLOGIES FOR THE COMMON GOOD

Executive summary from a report co-published by the Center for Genetics and Society and Friends of the Earth

The idea of genetically modified children was once the stuff of science fiction, but recent developments in genetic engineering and "synthetic biology" could make it a reality.

Scientists are bringing together a new generation of technologies that enable them to artificially redesign life – everything from yeast cells to people. And now, with recently developed techniques for "gene editing," the prospect of redesigning humans is much closer.

This is a brief overview of the current range of synthetic biology techniques and approaches, particularly gene editing, that are being proposed for use on humans. We discuss the challenges and concerns that arise from these proposals, including their unprecedented ethical, social and health implications.

Researchers hail synthetic biology – a new set of genetic engineering techniques – as "the future of manufacturing, engineering and medicine."[1] Amid big dreams are fast-paced investments. The synthetic biology market is expected to reach close to $39 billion by 2020.[2] Already products of synthetic biology, such as synthetic biology-derived vanillin, stevia and oils, are entering food and consumer products ahead of independent environmental and safety assessments, oversight and labeling – a worrying precedent for human applications.

But much more far-reaching proposals are in the pipeline. For example, one prominent synthetic biologist, Stanford's Drew Endy, has asked, "What if we could liberate ourselves from the tyranny of evolution by being able to design our own offspring?"[3]

Prominent voices, including some scientists working in the field, are deeply concerned about the unforeseen consequences that human genetic engineering could have. Some believe there are lines that should not be crossed, especially attempts to create genetically modified human beings (sometimes called "designer babies"), and suggest that the risks to individuals and to society will never be worth any supposed benefit. Others argue that if it's "safe," anything goes. A few even hypothesie that humanity will have a moral duty to genetically "enhance" our children if the technology and underpinning genetics progress.

No matter which opinion one holds, everyone needs to be aware of these new technologies and be able to engage in decisions about what is safe, ethical and beneficial.

There is a dearth of oversight for the rapidly emerging frontier of this merger of engineering and biology. Historic precedent demonstrates that failure to ensure transparency, democratic input and practical regulatory oversight can give license to unethical research that manifests with unintended consequences resulting in harm. Only in retrospect have these transgressions been made public.

For example, over a period of 40 years between 1932 and 1972, the US Public Health Service and the Tuskegee Institute engaged in unethical research, telling hundreds of black men that they were receiving treatment for syphilis, when in fact researchers were studying the impacts of the disease as it went untreated.[4] In the 1940s, US government medical researchers infected people in Guatemala with gonorrhea and syphilis without consent.[5]

More recently, there have been instances where either self-regulation has failed or scientists have not cooperated with government regulators. For example, some fertility clinics have routinely failed to follow existing professional guidelines regarding payment for women's eggs, social sex selection and the number of embryos transferred.[6] Cases of fraud and abuse have been documented from unregulated, unlicensed stem cell clinics that continue to proliferate, particularly off-shore.[7] In the late 1990s and early 2000s, several patients died as a result of unexpected reactions in gene therapy experiments.[8] In the follow-up to that tragedy, the National Institutes of Health discovered that "only 35 to 37 of 970 serious adverse events" in one kind of gene therapy trial were reported as required.[9]

The implications and potential impacts of gene editing are vast and in many cases, irreversible.

We need broad-ranging, inclusive discussions that expand beyond the ivory towers of academia or corporate-funded experts in the field, and that actively involve and integrate the perspectives of the public, including civil society organisations, labor unions, the faith community and others. The Center for Genetics and Society and Friends of the Earth-US advocate that everyone should have a voice in such monumental decisions about the future direction of humanity. Open, meaningful and full public participation at every level is essential and must include consideration of the wide-ranging ethical, social and economic impacts of these technologies alongside currently uncertain predictions around safety.

We are already seeing attempts to pave the way for genetically engineered humans. Consider this sequence of recent events:

- In April 2015, researchers from Sun Yat-sen University reported that they had used gene editing techniques to alter human embryos,[10] the first time in history this is known to have occurred.[11]
- In April and May 2015, many US scientists, as well

as the White House, National Institutes of Health and other agencies, called for a moratorium on experimenting with human embryos, and the National Academies of Sciences announced plans for a meeting to discuss the implications of this research in December 2015.[12]

- In September 2015, a group of six major UK research funders and the Hinxton Group, an international consortium on stem cells and ethics, both released statements advocating for gene editing research in human embryos.[13]
- Also in September 2015, a team of researchers affiliated with the Francis Crick Institute applied to the UK's Human Fertilisation and Embryology Authority for a license to begin genome editing research in human embryos.[14]

Together, these developments suggest that researchers may be much closer to heritable human applications of gene editing than previously thought, and that addressing the related social, environmental, health and ethical concerns is now critical.

Recent genetic engineering discussions have focused on CRISPR/Cas9, a molecular complex intended to "edit" a genome by cutting out and/or splicing in parts of DNA sequences. This technique (which is not yet perfected, but is rapidly being refined) is promoted as a promising tool to prevent genetic diseases.

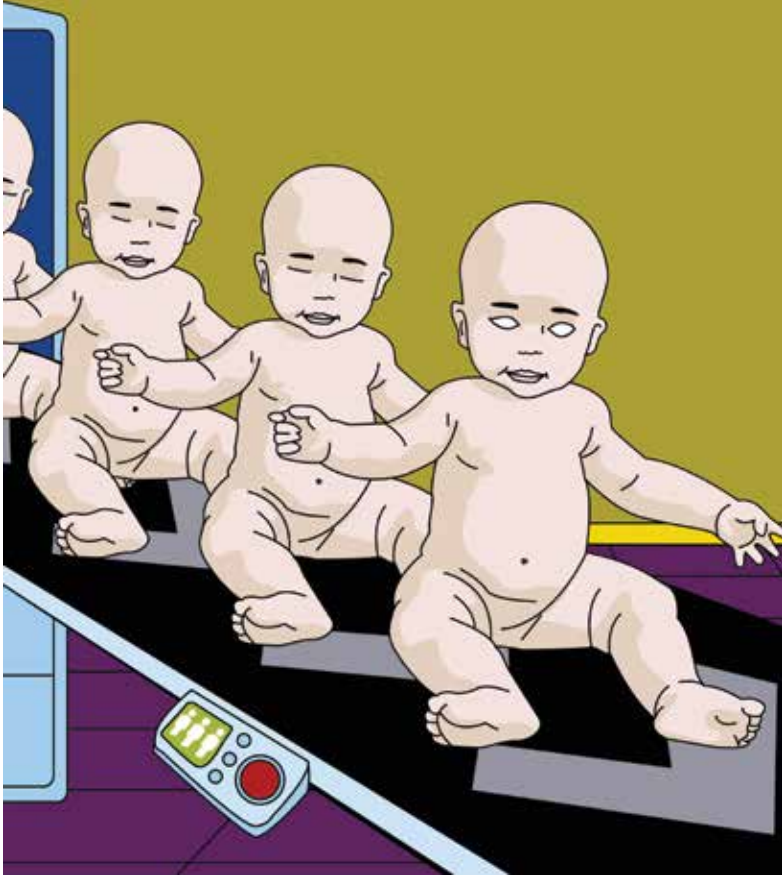
Using gene editing at the request of health-impacted patients with specific diseases, often referred to as "somatic" gene therapy, may be a worthwhile goal, if it is in fact feasible, and if the implications of such procedures are fully understood and accepted. But using the same techniques to modify embryos in order to make permanent, irreversible changes to future generations and to our common genetic heritage – the human germline, as it is known – is far more problematic.

Even the developers of the CRISPR/Cas9 tool are concerned about how others may use it. One of the discoverers, University of California, Berkeley researcher Jennifer Doudna, said:

> *"Once the discovery is made, it's out there. Anybody with basic molecular biology training can use it for genome editing. That's a bit scary."*[15]

In order to fully understand the implications of these technologies, there are essential questions that must be addressed:

- What might be the unforeseen consequences of editing DNA, about which scientists still understand very little?
- What if something goes wrong? With gene "editing" there is no simple "undo" button.
- Which of the proposed human engineering applications could address important problems?
- How can we avoid harms caused by a rush for new opportunities for profit?
- What are the risks of intervening in a patient's genome?
- Who has access and will benefit from these proposed applications?
- How do we evaluate assumptions about disease prevention, disabilities or the social creation of genetically modified humans?
- What is ethical, and who decides?



The implications and potential impacts of gene editing are vast and in many cases, irreversible.

The potential human applications of synthetic biology tools, such as gene editing, put big questions on the table. It is important to look at the assumptions we are making and to quickly raise awareness about how these technologies may impact our own DNA and health, and that of future generations.

FINDINGS AND KEY CONCERNS

- There are significant scientific, environmental, health and ethical challenges to the human applications of synthetic biology, which currently include reengineering the human microbiome, gene drives, xenotransplantation and gene editing.
- Science and biotechnology developed in the context of private funding, public investment, intellectual property and commercial pharmaceuticals is subject to systemic incentives to rush newly discovered technologies to market, regardless of their social utility and ahead of appropriate, transparent assessment and oversight.
- Heritable genetic modification in humans, also known as human germline intervention, is exceedingly difficult to justify on medical grounds, and carries enormous risks, both for individuals and society.

- Some of those who are advocating for moratoria on editing the human germline nonetheless limit discussions of "ethics" to questions of scientific risk (safety), and fail to significantly consider social, ethical and legal risks.
- The advent of human germline intervention could lead to the development of new forms of social inequality, discrimination and conflict. Among the risks of heritable genetic modification is the possibility of a modern version of eugenics, with human society being divided into genetic "haves" and "have-nots."
- Dozens of countries, including many of those with highly developed biotechnology sectors, have explicitly banned heritable human genetic modification, as has the Council of Europe's binding 1997 *Convention on Human Rights and Biomedicine*.

A CALL TO ACTION

We call for:

- National and international prohibitions on the use of gene editing and synthetic biology to alter the human germline for reproductive purposes. This call is especially relevant in those countries, like the US, that have not already enacted such a prohibition.
- Explicit and expansive public engagement on the human applications of synthetic biology, including consideration of not just safety thresholds, but also of social and ethical concerns.
- An ongoing, transparent, democratic process with which to evaluate and appropriately regulate new, emerging and proposed human applications of synthetic biology. This broad public oversight will hold scientists and entrepreneurs accountable to responsible regulation of these potentially hazardous technologies.
- Increased investment in more socially just and less risky solutions to environmental, health and social problems.

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Five reasons we should embrace gene editing research on human embryos

Future people would be grateful if their disease is cured, rather than being replaced by a different healthier or non-disabled person, notes bioethicist Julian Savulescu

Scientists from around the world are meeting in Washington this week to debate how best to proceed with research into gene-editing technology.

Gene editing is a new precise form of genetic engineering. It uses enzymes from bacteria to locate genes within DNA and delete or replace them. In early 2015, Chinese scientists used it to modify human embryos as a first step towards preventing the genetic transmission of a blood disease.

Many people, including scientists, are worried about creating genetically modified humans. They're worried about numerous things: genetic mistakes being passed on to the next generation; the creation of designer babies who are more intelligent, more beautiful or more athletic; and the possibility of causing severe growth abnormalities or cancer.

While these are valid concerns, they don't justify a ban on research. Indeed, such research is a moral imperative for five reasons.

1. Curing genetic diseases

Gene editing could be used to cure genetic diseases such cystic fibrosis or thalassaemia (the blood disease that the Chinese researchers were working to eliminate). At present, there are no cures for such diseases.

Detractors say selection of healthy embryos or fetuses via genetic testing is preferable. But such genetic tests require abortion or embryo destruction, which is also objectionable to some people.

What's more, genetic selection doesn't benefit patients – it's not a cure. It merely brings a different person, who is free from disease, into existence. Future people would be grateful if their disease is cured, rather than being replaced by a different healthier or non-disabled person.

2. Dealing with complex diseases

Most common human diseases, such as heart disease or schizophrenia, don't just involve one gene that's abnormal (such as in cystic fibrosis). They're the result of many, sometimes hundreds, of genes combining to cause ill health.

Genetic selection technologies can't eliminate genetic predispositions to these diseases. In principle, gene editing could be used to reduce the risk of heart disease or Alzheimer's disease.

3. Delaying or stopping ageing

Each day, thousands of people die from age-related causes. Cardiovascular disease (strongly age-related) is emerging as the biggest cause of death in the developing world. Ageing kills 30 million every year.

That makes it the most under-researched cause of death and suffering relative to its significance. Indeed, age-related diseases, such as heart disease or cancer, are really the symptoms of an underlying disease: ageing.

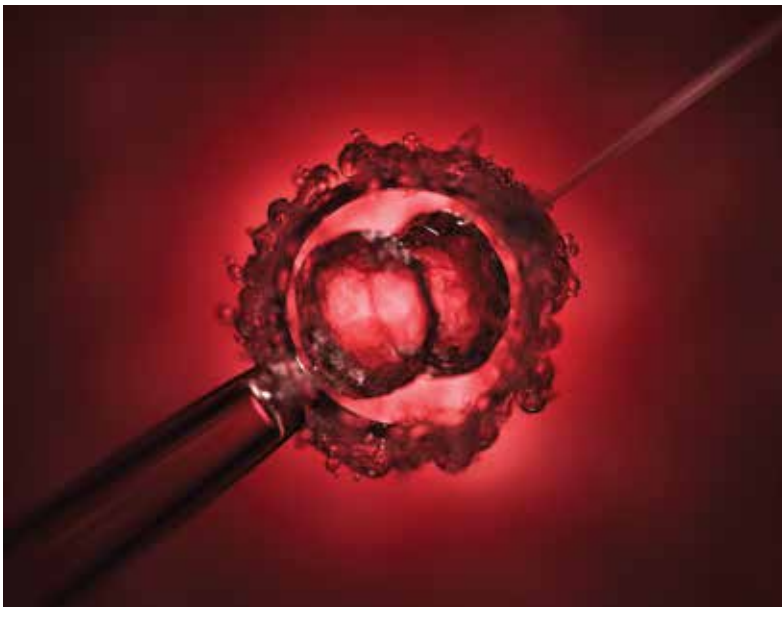
Gene editing could delay or arrest ageing; this has already been achieved in mice. Gene editing might offer the prospect of humans living twice as long, or perhaps even hundreds of years, without loss of memory, frailty or impotence.

4. Stopping the genetic lottery

The fourth reason for supporting gene-editing research on human embryos is the flip side of the designer baby objection. People worry that such technology could be used to create a master race, like fair-haired, blue-eyed "Aryans".

What this concern neglects is that the biological lottery – i.e. nature – has no mind to fairness. Some are born gifted and talented, others with short painful lives or severe disabilities. While we may worry about the creation of a genetic masterclass, we should also be

Many people, including scientists, are worried about creating genetically modified humans. They're worried about numerous things: genetic mistakes being passed on to the next generation; the creation of designer babies who are more intelligent, more beautiful or more athletic; and the possibility of causing severe growth abnormalities or cancer.



concerned about those who draw the short genetic straw.

Diet, education, special services and other social interventions are used to correct natural inequality. Ritalin, for example, is prescribed to up to 10% of children with poor self-control to improve their educational prospects and behavioural control.

Gene editing could be used as a part of public health care for egalitarian reasons: to benefit the worst off. People worry that such technologies will be used to benefit only those who can afford it – keep reading for why they shouldn't.

5. Making disease treatments less costly

Gene editing of human embryos could enable greater understanding of disease and new treatments that don't modify human beings.

Gene-edited embryonic stem cell lines that cause or protect against disease could help us understand the origins of disease. Other edited stem cells could help treatment – imagine blood cells that kill and replace leukemic cells.

This knowledge could be used to develop treatments for diseases, including drugs, that can be produced cheaply. And that would reduce, rather than increase, inequality.

Laws to prevent reproductive gene editing may be justified on the basis of safety concerns but a ban on therapeutic gene editing cannot. To ban it would be to ignore a great deal of good that can be done for a great many people, including some of the most vulnerable.

The moral imperative

There are valid concerns about applying gene editing to create live born babies. Such reproductive applications could be banned.

But the technology could be used for therapeutic research: to understand disease and develop new treatments. And any constraints we place on it must keep this in mind.

Laws to prevent reproductive gene editing may be justified on the basis of safety concerns but a ban on therapeutic gene editing cannot.

To ban it would be to ignore a great deal of good that can be done for a great many people, including some of the most vulnerable.

DISCLOSURE STATEMENT

Julian Savulescu does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond his academic appointment.

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THE CONVERSATION

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GENOME EDITING POSES ETHICAL PROBLEMS THAT WE CANNOT IGNORE

In the future, our DNA could be different by design, write ethicists

Anthony Wrigley and Ainsley Newson

The ability to precisely and accurately change almost any part of any genome, even in complex species such as humans, may soon become a reality through genome editing. But with great power comes great responsibility – and few subjects elicit such heated debates about moral rights and wrongs.

Although genetic engineering techniques have been around for some time, genome editing can achieve this with lower error rates, more simply and cheaply than ever – although the technology is certainly not yet perfect.

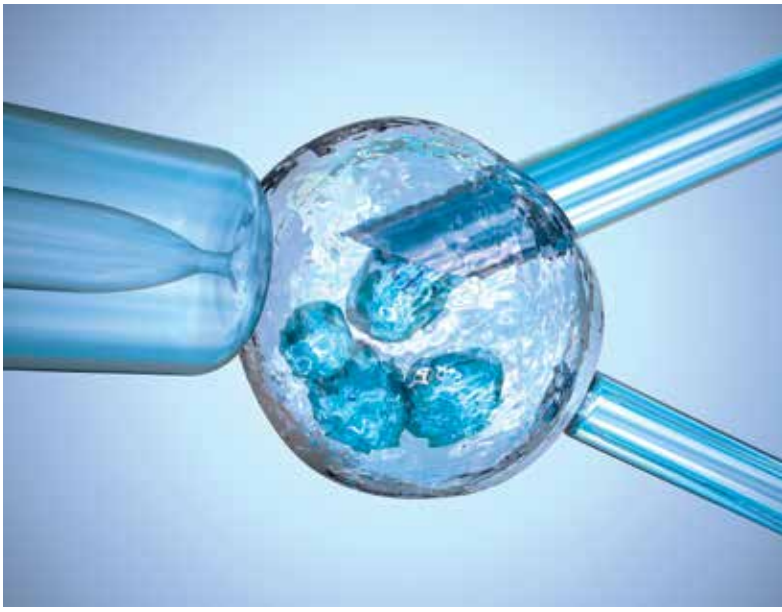
Genome editing offers a greater degree of control and precision in how specific DNA sequences are changed. It could be used in basic science, for human health, or improvements to crops. There are a variety of techniques but clustered regularly inter-spaced short palindromic repeats, or CRISPR, is perhaps the foremost.

CRISPR has prompted recent calls for a genome editing moratorium from a group of concerned US academics. Because it is the easiest technique to set up and so could be quickly and widely adopted, the fear is that it may be put into use far too soon – outstripping our understanding of its safety implications and preventing any opportunity to think about how such powerful tools should be controlled.

THE ETHICS OF GENETICS, REVISITED

Ethical concerns over genetic modification are not new, particularly when it comes to humans. While we don't think genome editing gives rise to any completely new ethical concerns, there is more to gene editing than just genetic modification.

First, there is no clear consensus as to whether genome editing is just an incremental step forward, or whether it represents a disruptive technology capable of overthrowing the current orthodoxy. If this is the case – and it's a very real prospect – then we will need to carefully consider genome editing's ethical implications, including whether current regulation is adequate.



Second, there are significant ethical concerns over the potential scope and scale of genome editing modifications. As more researchers use CRISPR to achieve more genome changes, the implications shift. Our consideration of a technology that is rarely used and then only in specific cases will differ from one that is widely used and put to all sorts of uses.

> *While we don't think genome editing gives rise to any completely new ethical concerns, there is more to gene editing than just genetic modification.*

Should we reach this tipping point, we will have to revisit the conclusions of the first few decades of the genetic modification debate. Currently modifying plants, some animals, and non-inheritable cells in humans is allowed under strict controls. But modifications that alter the human germ-line are not allowed, with the exception of the recent decision in the UK to allow mitochondrial replacement.

While this may mean weighing up potential benefits, risks and harms, as the potential applications of genome editing are so broad even this sort of assessment isn't straightforward.

USE FOR GOOD AND FOR ILL

Genome editing techniques have so far been used to change genomes in individual cells and in entire

(non-human) organisms. Benefits have included better targeted gene therapy in animal models of some diseases, such as Duchenne Muscular Dystrophy. It's also hoped that it will lead to a better understanding of the structure, function and regulation of genes. Genetic modification through genome editing of plants has already created herbicide- and infection-resistant crops.

But more contentious is how genome editing might be used to change traits in humans. While this has been the basis for many works of fiction, in real life our capacity to provide the sort of genetic engineering seen in films and books such as *Gattaca* and *Brave New World* has been substantially limited.

Genome editing potentially changes this, presenting us with the very real possibility that any aspect of the human genome could be manipulated as we desire. This could mean eliminating harmful genetic conditions, or enhancing traits deemed advantageous, such as resistance to diseases. But this ability may also open the door to eugenics, where those with access to the technology could select for future generations based on traits considered merely desirable: eye, skin or hair colour, or height.

PERMANENT EDITS

The concern prompting the US academics' call for a moratorium is the potential for altering the human germ-line, making gene alterations inheritable by our children. Gene therapies that produce non-inheritable changes in a person's genome are ethically accepted, in part because there is no risk for the next generation if things go wrong. However to date only one disease – severe combined immunodeficiency – has been cured by this therapy.

Germ-line alterations pose much greater ethical concerns. A mistake could harm future individuals by placing that mistake in every cell. Of course the flip-side is that, if carried out safely and as intended, germ-line alterations could also provide potentially permanent solutions to genetic diseases. No research is yet considering this in humans, however.

Nevertheless, even if changes to the germ-line turn out to be safe, the underlying ethical concerns of scope and scale that genome editing brings will remain. If a technique can be used widely and efficiently, without careful oversight governing its use, it can readily become a new norm or an expectation. Those unable to access the desired genetic alterations, be they humans with diseases, humans without enhanced genetic characteristics, or farmers without genetically modified animals or crops, may all find themselves gravely and unfairly disadvantaged.

DISCLOSURE STATEMENT

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World's first three-parent baby raises questions about long-term health risks

This story is the beginning of a new treatment with massive potential for good. However, rigorous regulation and checks are needed, writes Joanna Poulton

A baby boy, the first child to be born using a new technique that incorporates DNA from three people, is now five months old. It is great news – the birth of a healthy baby conceived by this new procedure is a major step forward and will lead to a new way of preventing the inheritance of mitochondrial diseases.

Mitochondria are the powerhouses of cells. They generate energy for all life processes. One in 400 people has a maternally-inherited mutation in mitochondrial DNA (mtDNA), the blueprint for some vital mitochondrial components. MtDNA mutations can cause a range of illnesses, including deafness, blindness, diabetes, and heart and liver failure. People with these disorders usually have both normal and damaged mtDNA, the symptoms being generally worse the higher the dose of damaged mtDNA. Sadly, there are no cures.

In Mitochondrial replacement therapy (MRT), embryos of the couple at risk of having an affected child are generated in a test tube. In this case, the nucleus that contains all of the genetic material apart from the mitochondria was removed from the mother's egg and placed into an egg with healthy mitochondria, from which the nucleus had been removed. The egg was then fertilised with the father's sperm and the resulting embryo was placed in the mother's womb where it developed into the baby.

This means the baby has three genetic parents: the father who supplied the sperm, the mother who supplied both womb and the egg nucleus, and an anonymous donor who supplied healthy mitochondria. Of these, the mitochondrial DNA is by far the smallest contribution. This type of three-parent baby is new, although other types have existed for many years.

MRT is being developed by groups in the UK and US to help the families of patients who have mitochondrial disease with a high recurrence risk in future children.

Unknown long-term effects

While experiments on monkeys and mice suggested that such babies would probably be healthy, this procedure hadn't been used in humans until now.

Eggs are highly organised cells. Replacing the nucleus does not prevent development into a baby, but it causes damage to the cell that probably requires radical re-organisation. So, the effects of such manipulations are still unknown and could cause problems later in life, such as an increased chance of diabetes.

According to a *New Scientist* report, the mother of the child, a Jordanian woman, had been trying for a family for 20 years. Her two children both died of Leigh syndrome – aged eight months, and six. The woman had a high risk of having further affected children.

In many countries, the mother would have been given other choices before MRT was offered. First, she would have been offered eggs from an unrelated healthy donor. These could be fertilised with her partner's sperm and put into her womb, preventing transmission of the mitochondrial disease completely. The woman with mtDNA disease is then the biological but not the genetic mother. Being born to a woman who is not your genetic parent may be acceptable to some people, given that perhaps up to one in 10 people in the UK do not identify their genetic fathers correctly – but it may have been unacceptable to this family.

She would have also been offered pre-implantation genetic diagnosis whereby several embryos can be tested at an early stage and the best one selected to be placed in the mother's womb. However, this was reportedly not ethically acceptable to this family.

The birth of a healthy baby after this technique is a big step forward. In the past related manipulations to improve "oocyte mitochondrial quality" have been carried out – so called "ooplasm donation" which involves donor mitochondria that

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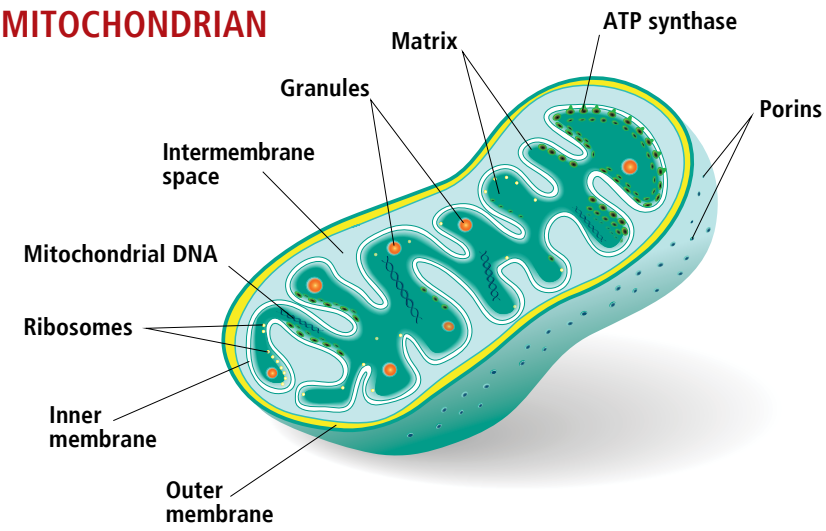


are injected into a germ cell in the ovary (an oocyte). But this procedure reportedly caused genetic defects and perhaps autism in one case.

While it is not yet possible to give the latest baby a decisive "all clear", he carries a low level of the damaging mutation, making it highly unlikely that he will develop Leigh syndrome.

The known unknowns

However, there are two more details of the story that could affect what happens next. First, the procedure could be termed "medical tourism": it was done in Mexico by a team based in New York City, so it was not covered by US regulations, which do not permit the procedure. The Institute of Medicine's Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases declined to give regulatory approval for clinical use of the procedure until research to answer critical safety and efficacy questions has been done.

Another problem is that we are not told how high the level of damaging mtDNA was in the mother's egg before the procedure was carried out – a detail that indicates how likely the child was to be severely affected at the outset.

If the level and hence the risk was high, this is a laudable technical advance that has massively reduced the child's chance of suffering a severe illness. If the level was low and compatible with a healthy life, then a procedure with significant unknowns might have been done unnecessarily – illustrating how much we need regulation to protect the rights of the future child. Reports do not clarify these vital details.

This story is the beginning of a new treatment with massive potential for good. However, rigorous regulation and checks on the unknowns of this new and controversial technology are needed.

DISCLOSURE STATEMENT

Joanna Poulton is affiliated with the University of Oxford. She has received funding from MRC.

Joanna Poulton is Professor, University of Oxford.

THE CONVERSATION

Poulton, J (28 September 2016). *World's first three-parent baby raises questions about long-term health risks.* Retrieved from http://theconversation.com on 19 September 2017.

HANDS OFF OUR GENES

An opinion piece by Adrian Rollins for the Australian Medical Association

Attempts by commercial operators to patent human genes have been dealt a blow after Australia's highest court overturned a patent awarded to a US-based company claiming rights to two cancer genes. In a decision with important international implications, the High Court has supported an appeal by two-time cancer survivor Yvonne D'Arcy after biotech company Myriad Genetics won Federal Court recognition of a patent for its discovery of the BRCA genes, which are linked to an increased risk of breast and ovarian cancer.

The company argued that by identifying and isolating the BRCA1 and BRCA2 gene – often referred to as the Jolie-genes after actress Angelina Jolie, who in 2013 revealed she had a mastectomy after it was found she had the variant – it had a patentable invention. It used its discovery to assert a monopoly over tests for the BRCA1 and BRCA2 gene, holding the cost of diagnosis up.

The Federal Court had supported Myriad's claim, judging that the discovery of the gene fell within the definition of manufacture. But the High Court found differently. In a unanimous decision, the judges said that, "While the invention claimed might be, in a formal sense, a product of human action, it was the existence of the information stored in the relevant sequences that was an essential element of the invention as claimed".

The High Court ruling follows a similar defeat for Myriad in a case in the US Supreme Court two years ago. The decision marks the end of a lengthy legal battle for Ms D'Arcy and her legal team, which had argued that genetic material is a product of nature and cannot be patented. Ms D'Arcy said the High Court's decision would make cancer testing more affordable.

"For all those people who do have the genetic footprint for breast cancer, or any cancer basically, it's a win for them because now they're forewarned," she told the ABC. "The testing will be a lot cheaper and it will be more available ... rather than using only Myriad's agents at a price that nobody really can afford. I'm just hoping that other countries will see sense and follow us and the Americans."

While the case is likely to lead to cheaper BRCA cancer tests for many, the High Court's ruling has raised concerns that it could stifle genetic research by denying commercial enterprises rights to discoveries they make.

Australian Medical Association (19 October 2015). *Hands off our genes.* Retrieved from http://ama.com.au on 19 September 2017.

Personalised medicine has obvious benefits but has anyone thought about the issues?

Personalised medicine allows treatment to be tailored to a patient's unique genetic makeup. However, once genetic testing and personalised therapies become more widely available, how do we ensure it is for the right reasons, asks Nola Ries and Dianne Nicol

Consumers, health care professionals and regulators must try to separate the rorts from evidence-based practice.

US Vice President Joe Biden recently launched The Genomic Data Commons, an open-access database that contains genomic and clinical data of 12,000 patients.

The aim is to allow researchers to better understand cancer's development, which will help tailor treatments to individuals' particular cancers.

This kind of approach is called personalised medicine and is said to be the next frontier in health care. A recent study in the journal *Nature*, for instance, reported groundbreaking research on the genetic causes of breast cancer. The study's lead author described it as "a step closer to personalised health care for cancer".

Personalised medicine has many benefits, such as treatment for cancers previously considered untreatable. This high-tech medical field also presents some regulatory problems, as outlined by a group of international experts – of which we were part – in the *Journal of Law and the Biosciences*.

These are:

- **Personal privacy** – the genetic research and testing needed for personalised medicine reveals people's deepest genetic secrets
- **Consumer protection** – a growing private industry is selling genetic tests to consumers, sidestepping the traditional relationship between doctor and patient
- **Health care costs** – worries about genetic risk factors for disease drive some people to undergo costly, and possibly unnecessary, tests and treatments.

Personal privacy

To find out how genes contribute to diseases, large collections of human tissue, blood, urine and saliva are stored in repositories called biobanks. Biobanks – much like the Genomic Data Commons – can be set up by public or private sector entities, such as government health departments, university research institutes and even drug companies. Researchers can then access the biobank collections for a variety of projects.

Members of the public and people with specific conditions "participate" in biobanks by donating their materials. A research team or a health care provider might invite them to participate. Participants are asked to share personal details about their lifestyle and medical and family history.

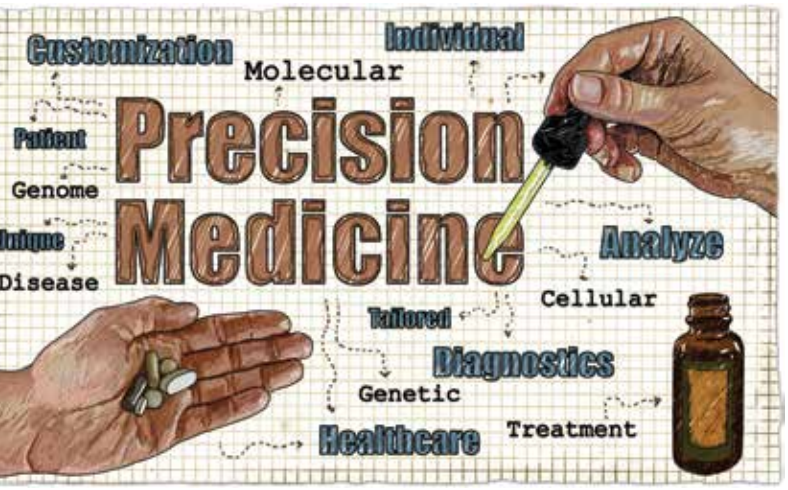
UK Biobank is a leading international example. It holds biological samples from half-a-million people. Closer to home, the Australasian Biospecimen Network is a network of 35 domestic and international biobanks for cancer research.

People become participants in biobanks without knowing what their genes might reveal and how researchers will use them in the future. Research studies can uncover a person's genetic future – such as a predisposition to Alzheimer's disease – and genetic past, including ancestry details.

Many of the non-profit biobanks, like UK Biobank, ask people to give broad consent for use of their materials in unspecified future health studies, including after their death.

These types of biobanks have established their own robust governance frameworks to ensure that laws and ethical principles are followed and participants' wishes are respected. However, this kind of regulation doesn't apply everywhere.

In a high-profile case a few years ago, Arizona State University agreed to return blood samples to the Havasupai Indian tribe after complaints that



Existing laws that forbid misleading commercial practices, protect personal privacy and establish frameworks for reviewing new drugs and treatments may be adequate, at least in the short term. But as the field of personalised medicine develops, governments may need to change laws and policies to promote safe and cost-effective use.

researchers had used the samples for genetic studies without the tribe's agreement.

Consumer protection

Health care in the genomic era involves new relationships between the individual and key players in the biomedical sector, including diagnostics (medical testing), drug industries and health care professionals.

Consumers can buy genetic tests from private companies without the advice of a doctor or genetic counsellor. Businesses peddle nutritional products and cosmetics, claiming they act on people's genes to help them lose weight and maintain a youthful glow.

Consumers, health care professionals and regulators must try to separate the rorts from evidence-based practice. Dermatology researchers are investigating how genes affect what our skin looks like, so legitimate anti-ageing products may one day keep us young. And the field of pharmacogenomics already helps doctors tailor some drugs to increase the effectiveness of the therapy and reduce harmful side effects.

However, once genetic testing and personalised therapies become more widely available, how do we ensure it's for the right reasons?

Health care costs

The hope is that precision medicine will eventually enable more cost-effective care. Yet easy access to genetic testing could create a growing class of the "worried well" – people afraid their genetic makeup is a ticking time-bomb for future disease.

Angelina Jolie's public disclosure of her high genetic risk for breast and ovarian cancer prompted a spike in women seeking genetic testing. In the same way, people who buy genetic screening tests from online businesses may end up in their doctor's office wanting help to understand the results.

Initiatives like the Choosing Wisely campaign can help consumers and clinicians decide if a particular test or treatment is likely to offer benefits that outweigh potential harms. In a genomic era, we will need education on how to judge the value of genetic testing and gene-based medical interventions.

Regulating wisely

Existing laws that forbid misleading commercial practices, protect personal privacy and establish frameworks for reviewing new drugs and treatments may be adequate, at least in the short term. But as the field of personalised medicine develops, governments may need to change laws and policies to promote safe and cost-effective use.

Our expert group warned against over-regulation, which may stifle genomics research and the translation of findings into new therapies. Trust between the public, biobanking organisations and researchers is crucial. Public trust is likely to be challenged when there is commercial involvement, either in the biobank itself or the research it supports. Biobanks should be transparent about their activities and tell people up front the terms on which researchers can use stored samples.

Health care providers are no longer gatekeepers between patients and their genetic information. But they will need the knowledge and skills to help people understand genetic risks and decide when personalised medicine may be an appropriate option for their care.

DISCLOSURE STATEMENT

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Nola Ries is Senior Lecturer, University of Newcastle.
Dianne Nicol is Professor of Law, University of Tasmania.

THE CONVERSATION

Ries, N and Nicol, D (17 June 2016). *Personalised medicine has obvious benefits but has anyone thought about the issues?* Retrieved from http://theconversation.com on 19 September 2017.

THE ETHICAL BOOGIEMAN OF THE EUGENICS REVOLUTION

Relax – eugenics doesn't need to be a dirty word anymore, argues Nicholas Evans

Every time a new technology emerges with the capacity to change human genetics, a concern arises that the quest to improve human life will ultimately lead to governments exerting control over who gets born or who reproduces. This fear trades in images of Nazis, of "perfect" humans (usually Jude Law and Uma Thurman) in a world without freedom. The fear is captured in a term commonly and not unreasonably associated with oppression: *eugenics.*

But the technologies we associate with eugenics aren't obviously terrible. A successful mitochondrial DNA transfer, which leads to what have mistakenly been called "three-parent babies", has been described as a kind of eugenics. The technology is being used to cure a rare, heritable and often fatal disease. Human germ line editing – which enables scientists to accurately remove or replace strands of DNA – sounds like a firm step towards eugenics.

Is it possible eugenics isn't always obviously bad?

The forces of eugenics pervade our science and technology and our conceptions of wellness in ways we might not have anticipated but need to consider.

In the past, eugenics combined bad science with bad politics: a politics that was grassroots as much as it was government sanctioned. In the United States at the end of the 19th century, eugenics was a civil religion: famous lawmakers, activists and individual people in the street had positive views of what eugenics could accomplish. As late as the 1981, Oregon was still forcing sterilisation on the "unfit".

These views and interventions were misguided attempts to solve social violence, poverty and "feeble-mindedness" – what we would now call disability. The politics were racist, the notions of genetic purity wrongheaded. Believe it or not, the science was even worse.

These days, we've got much better science. But I'd suggest it's an open question whether our politics have kept up with the technology. Given the resurgence of One Nation in Australia, the 'death of expertise' during Brexit in the UK, and a certain orange-haired ideologue's run for office in the United States, the answer might well be "no".

> *The germ from which eugenics grows is our society's relationship to the idea of human health – so this is the question we need to tackle most urgently.*

Either way, the forces of eugenics pervade our science and technology and our conceptions of wellness in ways we might not have anticipated but need to consider.

DESIGNER BABIES AND THE 'DISEASE OF AGEING'

The first challenge starts with the idea death is a disease. That's the view of George Church, a biologist at Harvard University who is engaged in the search to stop ageing and the challenges of an ageing population. Funded by Google and with the support of biologists and philosophers who share his vision, Church is out to not just relieve the ill health that comes with growing old, but the condition of growing old itself.

It sounds too good to be true and it may just be a billion dollar pipe dream, but other technologies might also help combat issues associated with ageing. Right now, parents can use preimplantation genetic diagnosis to select embryos without debilitating inherited diseases, such as Huntington's disease. Scientists are looking hard for the genetic basis of Alzheimer's disease and other forms of dementia and we could one day select our children to have less risk of dementia or other common end of life diseases.

These are fundamentally eugenic ideas. That's not to say they are bad ideas: dementia is considered a public health crisis, with the combined costs of having dementia

and caring for someone with dementia predicted to exceed $1 trillion by 2018.

Nothing is wrong, in principle, with wanting to avert the harms of social ill known as "the aging population", even through genetic means. If we could eliminate dementia through gene therapies and genetic selection, I think most of us would say this would be an unequivocally good thing. But this is eugenics: solving social ills through genetic selection and modification.

We often think about eugenics in terms of selecting our children's eye colour or intelligence. One day we may well face those problems. But the germ from which eugenics grows is our society's relationship to the idea of human health – so this is the question we need to tackle most urgently.

DISTRIBUTION, DISABILITY AND CHOICE

So if eugenics isn't just about the government, nor is it always bad, how should we think about it?

With caution.

In Australia, specialist medical services – including genetic testing and selection – are covered by Australian Medicare. This, in the world of the new eugenics, is a good thing. If there are genuine benefits to be had from genetic selection or gene therapy, they should be available to all.

A key concern about these new technologies is society splitting into genetic haves and have-nots. Right now, our society is stratified into medical haves and have-nots. A further breakdown into genetic haves and have-nots could be a social and political disaster. Ensuring our healthcare remains accessible is important – if there are savings to be made to healthcare, all the better.

With more complex traits, there may foreseeably be trade-offs between different genetic codes. What these might be, we can't be sure of just yet. A fanciful example would be mathematical intelligence and creativity. However the risk of modern tech culture driving the new eugenics is that these trade-offs will simply become trends until modern society doesn't respect anything but traits favoured by technocrats.

This would be a disaster: even the military takes all kinds of people. We already know society creates and reinforces disability. A threat of the new eugenics is that it will exacerbate disability by creating new ways to systematically exclude people from social life.

Even if we develop the power to change our genes, it doesn't follow that we should.

Finally, we need to think long and hard about the degree to which we come to think about genes as a product of choice. Even if we develop the power to change our genes, it doesn't follow we should have to. Valuing, and upholding a right to genetic diversity should become part of a recognised system of human rights, and we should make sure our medical and legal system guarantees care, even if the care is required as a result of 'preventable genetics'.

Nicholas Evans is Assistant Professor of Philosophy at University of Massachusetts Lowell.

Evans, N (3 November 2016). *The Ethical Boogieman of the Eugenics Revolution*. Retrieved from www.ethics.org.au on 19 September 2017.

EXPLORING ISSUES

WORKSHEETS AND ACTIVITIES

The Exploring Issues section comprises a range of ready-to-use worksheets featuring activities which relate to facts and views raised in this book.

The exercises presented in these worksheets are suitable for use by students at middle secondary school level and beyond. Some of the activities may be explored either individually or as a group.

As the information in this book is compiled from a number of different sources, readers are prompted to consider the origin of the text and to critically evaluate the questions presented.

Is the information cited from a primary or secondary source? Are you being presented with facts or opinions?

Is there any evidence of a particular bias or agenda? What are your own views after having explored the issues?

CONTENTS

Brainstorm, individually or as a group, to find out what you know about human genetics.

1. **What is a gene, and how many can be found in the human body?**

2. **What do the letters DNA stand for in relation to human genetics, and why is DNA important?**

3. **What is gene therapy, and how does it differ from genetic engineering?**

4. **What does the term 'eugenics' mean, and why is it controversial in relation to gene therapies?**

5. **What is meant by the term 'genetic discrimination', and what are some examples?**

Complete the following activities on a separate sheet of paper if more space is required.

1. **Genetic disorders fall under the following four broad categories: single gene disorders, choromosomal abnormalities, mitochondrial disorders and multifactorial disorders. Write a paragraph on each category including a description and at least two examples for each.**

2. **A human's genetic information can be thought of being made up of a two 'volumes' – one volume supplied by the biological father and the other by the biological mother. Write a few paragraphs explaining how these 'volumes' are made up, and what they contain? Include information on human cells, DNA, chromosomes and genes.**

Complete the following activity on a separate sheet of paper if more space is required.

Form into groups of two or more people to discuss the following topics related to human genetics and ethics. Using the spaces provided, discuss and compile a list of PROS and CONS for each topic. Discuss and share your pros and cons with other groups in the class.

GENETIC TESTING

"Genetic tests most commonly present an opportunity for individuals to become informed about their genetic predisposition to disease, and for couples to be aware of the possible genetic characteristics of their unborn children. Stemming from the informative potential of genetic testing some critical ethical, legal and social issues come to the forefront."

GENE EDITING

"Gene editing is a new precise form of genetic engineering. It uses enzymes from bacteria to locate genes within DNA and delete or replace them. In early 2015, Chinese scientists used it to modify human embryos as a first step towards preventing the genetic transmission of a blood disease."

THREE-PERSON IVF

"In mitochondrial replacement therapy (MRT), the baby has three genetic parents: the father who supplied the sperm, the mother who supplied both womb and the egg nucleus, and an anonymous donor who supplied healthy mitochondria."

Complete the following activities on a separate sheet of paper if more space is required.

"Recent genetic engineering discussions have focused on CRISPR/Cas9, a molecular complex intended to "edit" a genome by cutting out and/or splicing in parts of DNA sequences. This technique (which is not yet perfected, but is rapidly being refined) is promoted as a promising tool to prevent genetic diseases."

Center for Genetics and Society, ***Extreme Genetic Engineering and the Human Future.***

Use the internet to research the latest developments in CRISPR technology. Write a few paragraphs on at least two (2) of the most recent research developments using CRISPR techniques. Explain what CRISPR techniques are being used, what the developments are, who has developed them and what the potential benefits are expected to be.

"A recent study in the journal 'Nature' reported groundbreaking research on the genetic causes of breast cancer. The study's lead author described it as 'a step closer to personalised health care for cancer'."

Ries, N and Nicol, D, ***Personalised medicine has obvious benefits but has anyone thought about the issues?***

Use the internet to research the latest developments in personalised medicine (also termed precision medicine). Write a few paragraphs on at least two (2) of the most recent research developments using the personalised medicine approach. Explain what personalised medicine is, what the recent developments are, who has developed them and what the potential benefits are expected to be.

Complete the following multiple choice questionnaire by circling or matching your preferred responses. The answers are at the end of this page.

1. How many chromosomes are contained in the nucleus of most human cells?

a. 2
b. 13
c. 23
d. 46
e. 66
f. 73
g. 92

2. Which of the following letter combinations is used to represent a male and a female chromosome?

a. A and B
b. M and F
c. B and G
d. S and X
e. X and Y
f. Y and Z
g. Z and A

3. In what year did scientists announce that the first human genome sequence had been mapped in full?

a. 1966
b. 1978
c. 1981
d. 1995
e. 2003
f. 2017
g. None of the above (a human genome sequence has never been mapped in full).

4. Which of the following is the abbreviation for the agency that is responsible for approving genetically modified foods in Australia?

a. CSIRO
b. CRISPR
c. DNA
d. FSANZ
e. NHMRC
f. USFDA

5. Which of the following are the four basic building blocks of DNA? (select all four that apply)

a. Guanine
b. Melatonin
c. Adenine
d. Thymine
e. Cytosine
f. Niacin
g. Biotin

MULTIPLE CHOICE ANSWERS

1 = d; 2 = e; 3 = e; 4 = e; 5 = a, c, d, e.

- There are over 20,000 genes found in the DNA of each person. Each gene has its own specific location on a chromosome or on the mitochondrial DNA and the genes plus the non-coding DNA make up that person's genome (Centre for Genetics Education, *An introduction to DNA, genes and chromosomes*). (p.3)
- In most human cells, the genetic material is made up of long DNA strands that are packaged into 23 pairs of chromosomes (NHMRC, *The human genome*). (p.5)
- Mutations in inherited genes can result in genetic diseases or conditions that may cause problems at any stage of life, depending on the type of mutation (*ibid*). (p.5)
- The four broad groups of genetic disorders include single gene disorders, chromosome abnormalities, mitochondrial disorders and multifactorial disorders (Better Health Channel, *Genetic disorders*). (p.6)
- Genes are paired – one copy of each gene pair is inherited from the mother and the other copy from the father. Around 6,000 known genetic disorders are caused by inheriting an altered gene (*ibid*). (p.6)
- Genetic tests present an opportunity for individuals to become informed about their genetic predisposition to disease, and for couples to be aware of the possible genetic characteristics of their unborn children (WHO, *Human Genomics in global health: genetic testing*). (p.8)
- A growing number of genetic tests are available direct to the public, often over the internet. They are known as direct-to-consumer (DTC) genetic tests (NHMRC, *Medical genetic testing: health information for you and your family*). (p.12)
- Genetic tests that predict your risk for more common diseases may soon become readily available in the healthcare industry (Vinkhuyzen, A and Wray, N, *Why we should test everyone's genes to predict disease*). (p.15)
- Genomic testing takes advantage of recent advances in our knowledge of genetic causes of disease, as well as technology. It's a test of all 23,000 genes in the body at once (Amor, D, *Gene testing for the public: a way to ward off disease, or a useless worry?*). (p.19)
- In Australia, genetic information can be taken into account in applications for life insurance products such as cover for death or income protection because these types of insurance are 'risk rated' (NHMRC, *Genetic discrimination*). (p.21)
- Genetic counselling is essential both before and after genetic testing so that all the implications of undertaking testing including having information which might be of interest to others can be understood (Centre for Genetics Education, *Ethical issues in human genetics and genomics*). (p.25)
- 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 (Better Health Channel, *Gene therapy*). (p.27)
- Between 1989 and 2010, 1,698 clinical gene therapy trials were initiated or approved worldwide. So far, less than 1% of these have shown clinical benefit (*ibid*). (p.29)
- In 2003, scientists announced that the first human genome sequence had been mapped in full. The map took 13 years and more than US$3 billion in public funds to complete, and was one of the largest global scientific collaborations ever attempted. By 2016, a complete individual human genome could be sequenced in a day for US$1,000 (Dronov, R and Howard, W, *Gene editing and CRISPR*). (p.30)
- In 2006 the European Union and in 2009 the US FDA approved a breed of goat that produces an anti-clotting protein in its milk. In 2015, both agencies approved a genetically-modified chicken breed that expresses an anti-cholesterol drug in its eggs (*ibid*). (p.31)
- CRISPR could potentially prevent the spread of vector-borne diseases, such as dengue fever or malaria, by modifying mosquito populations through the use of 'gene drives' (*ibid*). (p.32)
- Research using human embryos is highly regulated, and is different between countries. In Australia, the NHMRC has a strict set of guidelines, meaning that all research performed on human embryos is monitored very closely, and many limitations exist (Brown, H, *Human embryo CRISPR advances science but let's focus on ethics, not world firsts*). (p.35)
- The synthetic biology market is expected to reach close to $39 billion by 2020 (Center for Genetics and Society, *Extreme genetic engineering and the human future*). (p.38)
- Dozens of countries, including many of those with highly developed biotechnology sectors, have explicitly banned heritable human genetic modification, as has the Council of Europe's binding 1997 *Convention on Human Rights and Biomedicine* (*ibid*). (p.40)
- CRISPR has prompted recent calls for a genome editing moratorium from a group of concerned US academics (Wrigley, A and Newson, A, *Genome editing poses ethical problems that we cannot ignore*). (p.43)
- To find out how genes contribute to diseases, large collections of human tissue, blood, urine and saliva are stored in repositories called biobanks. Biobanks can be set up by public or private sector entities, such as government health departments, university research institutes and even drug companies. Researchers can then access the biobank collections for a variety of projects (Ries, N and Nicol, D, *Personalised medicine has obvious benefits but has anyone thought about the issues?*). (p.47)
- A successful mitochondrial DNA transfer, which leads to what have mistakenly been called "three-parent babies", has been described as a kind of eugenics. The technology is being used to cure a rare, heritable and often fatal disease (Evans, N, *The ethical boogieman of the eugenics revolution*). (p.49)

GLOSSARY

Bioethics
The study of the ethical issues emerging from advances in biology and medicine. It is also moral discernment as it relates to medical policy and practice.

Chromosome
Thread-like structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.

CRISPR
Abbreviation for Clustered Regularly Interspaced Short Palindromic Repeats, which are the hallmark of a bacterial defence system that forms the basis for CRISPR-Cas9 genome editing technology.

DNA
Deoxyribonucleic acid (DNA) contains the genetic instructions used in the development and functioning of all cellular organisms.

Eugenics
A set of beliefs and practices that aims at improving the genetic quality of a human population.

Gene
Basic unit of heredity found in chromosomes. A gene is a section of DNA that controls a specific trait e.g. hair colour, eye colour, or blood type. In some cases, several genes interact to produce the final result.

Gene editing
Involves making precise changes to DNA in order to change a gene or the expression of a gene. This can be used to turn some genes 'on' or 'off' (a potential treatment for genetic disorders), or to enhance a particular trait (better crop yields).

Gene mutation
A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Gene therapy
In medicine, gene therapy (also called human gene transfer) is the therapeutic delivery of nucleic acid into a patient's cells as a drug to treat disease.

Genetic conditions
Many health or developmental conditions are due to either a variation in our genetic information or a combination of our genetic information and environmental causes such as diet, chemical exposure or lifestyle. Genetic conditions account for many of the health and development problems seen at birth, childhood, adolescence and adulthood.

Genetic discrimination
Occurs when people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder. Fear of discrimination is a common concern among people considering genetic testing.

Genetic testing
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.

Genome
The entirety of an organism's hereditary information.

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.

Human enhancement
Any attempt to temporarily or permanently overcome the current limitations of the human body through natural or artificial means. It is the use of technological means to select or alter human characteristics and capacities, whether or not the alteration results in characteristics and capacities that lie beyond the existing human range.

Human genetics
The study of inheritance as it occurs in human beings. Human genetics encompasses a variety of overlapping fields including: classical genetics, cytogenetics, molecular genetics, biochemical genetics, genomics, population genetics, developmental genetics, clinical genetics, and genetic counselling.

Human genome
The complete set of nucleic acid sequences for humans, encoded as DNA within the 23 chromosome pairs in cell nuclei and in a small DNA molecule found within individual mitochondria.

Mitochondrial replacement therapy
MRT (also called mitochondrial donation) is a special form of in vitro fertilisation in which the future baby's mitochondrial DNA comes from a third party. This technique is used in cases when mothers carry genes for mitochondrial diseases. The two most common techniques in mitochondrial donation are pronuclear transfer and maternal spindle transfer.

Personalised medicine
Also called precision medicine, it uses knowledge of a person's unique genetic make-up to predict disease development, to influence decisions about lifestyle choices or to tailor treatment to an individual.

Websites with further information on the topic

Better Health Channel www.betterhealth.vic.gov.au
Center for Genetics and Society www.geneticsandsociety.org
Centre for Genetics Education (NSW Health) www.genetics.edu.au
Department of Health (Australian Government) www.health.gov.au
Genetic and Rare Disease Network http://gardn.org.au
Genetic Alliance Australia www.geneticalliance.org.au
Human Genetics Society of Australasia www.hgsa.org.au
National Medical and Health Research Council www.nhmrc.gov.au
The Conversation www.theconversation.com/au

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THANK YOU

- Better Health Channel
- Centre for Genetics Education
- National Medical and Health Research Council.

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