

Editing Human DNA

Moral and social
implications of germline
genetic modification

Colophon:

This is a joint publication by the Netherlands Commission on Genetic Modification (COGEM) and the Health Council of the Netherlands.

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Summary

This report is about *germline genetic modification* (also called *germline modification*): altering or 'editing' the DNA of a human embryo. This technique offers people with genetic diseases new opportunities to have their own genetic children without the risk of passing on the disease.

Unlike somatic genetic modification, germline genetic modification involves altering the DNA in the whole embryo (and therefore in all the cells of the individual), which means that the modified DNA will be passed on to future generations.

In this report the Health Council of the Netherlands and COGEM describe the technical, legal and ethical issues raised by human germline modification. The main questions examined are:

- What is known about the effectiveness and safety of germline genetic modification in the short and long term, both for individuals and for society as a whole? What research is needed to clarify these issues?
- What is the legal and ethical framework for germline genetic modification? What aspects of the existing legal and ethical framework are being stretched by current developments in gene technology?
- How can the government, professional groups and society steer the governance of germline modification in an acceptable direction?

Questions such as these are now highly relevant given the rapid advances being made in germline modification following the discovery of the *Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 system* (CRISPR-Cas). Simply stated, this system is a tool for disabling and repairing individual genes and for cutting or adding pieces of DNA much faster and more efficiently than was previously possible. In short, it is a tool for putting germline genetic modification into practice.

The new possibilities opened up by germline modification offer prospects for treating and preventing genetic disorders. The benefits and risks of these applications of germline modification are currently being debated by patient organisations and scientists. The governments must therefore decide what position to take on these new possibilities and how to regulate germline modification. To ensure the good governance of germline modification there is an urgent need for a legal and ethical framework.

This report reviews the relevant scientific information and explores the legal, ethical and social aspects of germline modification. The Health Council of the Netherlands and COGEM have prepared this report to aid the House of Representatives, the Minister of Health, Welfare and Sport and the Minister of Infrastructure and the Environment in coming to an informed and balanced decision on which types of research and subsequent clinical applications of germline modification are acceptable. In addition, the Health Council of the Neth-

erlands, in its advisory role, makes some recommendations to the Minister of Health, Welfare and Sport.

Effectiveness and safety of germline genetic modification

In recent years, technologies similar to CRISPR-Cas have also been developed and are being used worldwide to make accurate, targeted changes in the genetic make-up of animals, plants and microorganisms. Very little research has yet been done with human embryos, but the techniques open up undeniable possibilities for medical applications. CRISPR technologies can be used to repair some genetic disorders, although the possibilities are not unlimited.

However, various scientific and technical issues still have to be resolved to remove or reduce the uncertainties still surrounding the mechanism and safety of the CRISPR technology used for germline genetic modification. These uncertainties include issues of *effectiveness* and *accuracy*: will the intended alterations to the genetic code always be done properly? A further uncertainty concerns the *efficiency* of the technique: for instance, what is the success rate and how many embryos will be needed on average to carry out a successful germline modification? The *long-term effects* of germline modification are also not known with any certainty.

It is important that thought is now given to how the long-term risks to individuals and subsequent generations can be investigated, and to how these long-term risks should be taken into consideration when deciding on potential clinical applications of germline modification.

The Legal framework for research into and applications of germline genetic modification

Further research is needed before gene-editing technologies such as CRISPR can be used for germline modification. *Surplus embryos* (embryos left unused after an assisted reproduction treatment, which in principle should be destroyed) could be used in fundamental research, for example on early embryonic development, or in preclinical research into the safety of new reproductive techniques. However, these embryos will not be sufficient. Human embryos will also have to be *cultured* specifically for research purposes.

At the moment, in the Netherlands culturing such embryos is prohibited under the Embryo Act. The reasoning behind this prohibition is that culturing embryos for research is considered to be a greater violation of respect for life than the use of surplus embryos for research purposes. However, in 2016 the Dutch government announced its intention to change these provisions in the Embryo Act to bring the Netherlands in line with other Western European countries, where the legislation on research involving embryos has become less restrictive in recent years. Revision of the Embryo Act should make it possible, under strict conditions, to produce embryos for scientific research purposes in the Netherlands as well.

Another legal restriction on the use of germline modification is that the Embryo Act limits the types of modifications that may be made to human DNA. Cell nuclear transfer is permitted, but embryos containing cells with a modified nucleus may not be implanted in the uterus. This means that clinical applications of germline modification are currently prohibited.

Ethical dilemmas surrounding germline genetic modification

Research into germline genetic modification also raises ethical questions. One of these questions is about *research on human embryos*. Such research involves interfering with the very earliest stage of human life and this affects fundamental values of varying significance to different groups of people. The question is how the intrinsic value of the human embryo is interpreted in terms of its right to protection. In the Netherlands it is assumed that the embryo has intrinsic value and as such deserves protection. The degree of protection afforded to the embryo increases as it develops, but is never absolute; other interests that carry greater moral force may outweigh the embryos right to protection. For different reasons, some people believe human embryos have a right to absolute protection and that every form of research involving human embryos is unacceptable. Others view embryos as nothing more than a form of human tissue, and for them embryo research presents no ethical problems at all.

Research into gene editing requires cultured embryos, but until now research has been permitted only on surplus embryos left over after assisted reproduction treatments. However, *distinguishing between cultured embryos and surplus embryos* is laden with ethical issues. Some people consider it morally unacceptable to create human life solely for scientific research. From this standpoint, research on surplus embryos is morally permissible because these embryos are created for an assisted reproduction treatment and therefore in principle each had a chance of developing into a person. However, there is no consensus on this question because most assisted reproduction treatments involve the creation of more embryos than are implanted in the uterus.

Clinical applications of human germline modification also involve ethical dilemmas concerning people's desire to have children that are genetically their own and whether or not germline modification is necessary for this (instead of an alternative such as embryo selection). There are also broader societal concerns about the desirability of germline modification: it could widen existing differences between people if the technology is available only to a select group. Finally, there is a debate about whether germline modification may be used for human 'enhancement' or that limits should be set on human genetic engineering.

It is unlikely that international consensus will be reached on these questions any time soon. With scientific advances in the field of germline modification now moving at such a fast pace, it is essential that these issues are put on the international agenda.

Points for consideration by government, scientists, medical professionals and society

When considering complex issues such as germline genetic modification it is important that the government, the scientific community and society as a whole agree on who decides what and when, and on the basis of what arguments. In other words, a system of good governance must be established for germline modification. This report discusses the points that need to be considered by the government, scientists, medical professionals and society.

For the *government*, the key question in the short term is whether or not to amend the Embryo Act and, if it should be amended, how it should be amended to take account of the latest scientific understanding and the public debate about the use of human embryos in research. In the longer term, there is the question of whether or not clinical applications of germline genetic modification should be permitted, and if so, under what conditions. In principle, these clinical applications will be to prevent serious diseases, but this raises questions of precisely which diseases are included and how these applications are to be differentiated from applications that have more to do with human enhancement. To answer these questions, use could be made of the regulatory framework currently in place for embryo selection.

The *scientific community* has a duty regarding the social implications of research into germline genetic modification. Some aspects of the safety and efficiency of the technology used are not simply technical or scientific in nature, but require broader stakeholder discussions with medical professions, patient associations and other social groups on questions such as: what is a harmful effect, what effects are unacceptable and what are the effects for society as a whole? Given the nature of the issues surrounding germline modification it is important that scientists speak up and explain why they do this type of research, or why they do not.

If germline modification becomes clinically available in future, *medical professionals* should provide full and balanced information about this treatment and the possible alternatives. In the longer term, any clinical applications of germline modification should be subject to good *governance*. This must cover things like whether or not the first children to be born with germline modifications will be monitored during their lives to identify and investigate any unanticipated effects, and if so, how. If germline modification and its clinical applications are not permitted in the Netherlands, 'medical tourism' will be a real possibility and should be taken into account.

Finally, *society* is not uniform and people's opinions can change. But that does not mean that the views of those involved and of the wider public are not important. Maintaining a record of all these differing opinions can be a useful tool for identifying issues of importance for governance and policymaking.

Advice and recommendations

The Health Council of the Netherlands advises the Minister of Health, Welfare and Sport to lift the prohibition on carrying out scientific research on specially created embryos to enable research on cultured embryos, under strict conditions, for certain purposes. This should include fundamental research into the use of CRISPR for germline genetic modification.

The Health Council of the Netherlands further advises the minister to amend the Embryo Act so that germline genetic modification and cell nuclear transfer are no longer considered to be fundamentally different. The Council is of the opinion that using either of these technologies to prevent serious diseases does not violate human dignity.

To ensure that both the medical and scientific communities and the general public remain involved in the further decision-making on the use of germline genetic modification, COGEM and the Health Council of the Netherlands recommend holding a social dialogue with scientists, practitioners and the wider public on lifting the prohibition on scientific research on cultured embryos.

1. Introduction

New techniques for genetic modification may make it possible in future to prevent genetic disorders from being passed on to the next generation. This would be an important advance, because in many cases the symptoms of genetic disorders or diseases have a major impact on the quality of life and the life expectancy of patients. At the moment, treatments are available for just a few genetic diseases and curing them is not yet possible and so the risk of these diseases being passed on via the genes is high. However, for people with some genetic diseases there are possibilities for having their own genetic children without the risk of passing on the disease: having a prenatal diagnosis and terminating the pregnancy if the child has the disease; having a pre-implantation genetic diagnosis (PGD) – also called embryo selection; using an egg or sperm donor; or adoption.

1.1 Germline genetic modification: altering DNA with consequences for descendants

A possibility that used to be merely theoretical is germline genetic modification of human embryos.^a Germline modification involves making targeted changes in the genome (DNA) of cells that make up the germline (stem cells for gametes, ova, sperm and embryonal cells). Changes made to germline cells are irreversible for the resulting individual and are passed on to future generations. Making such changes that remove or repair genetic diseases and disorders would therefore eradicate them from the DNA for good.

In this report, *germline genetic modification*, or simply *germline modification*, is used to mean the making of targeted alterations in the genome of the human embryo, unless stated otherwise. Until recently there was no efficient and accurate technology available for germline modification, but this changed with the discovery of the *Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 system* (CRISPR).

1.2 Breakthrough in gene editing: the CRISPR technology

Over the past few years the CRISPR gene-editing technology has taken the field of biotechnology by storm and is now used around the world to make precise, targeted alterations to the genomes of animals, plants and microorganisms.¹ This technology makes it possible, in principle, to switch off and repair genes and to remove or add pieces of DNA. CRISPR is a gene-editing technique, along with a number of other techniques such as zinc finger nuclease (ZFN) and transcription activator-like effector nucleases (TALENs). So far, CRISPR is the most efficient and accurate of the gene-editing techniques and has the widest range of possible applications. It opens up new possibilities for medical applications, both for the

^a A cell or cluster of cells with the potential to develop into a human being.

treatment of genetic disorders (e.g. somatic cell-gene therapy) and for repairing or preventing genetic disorders by making targeted alterations to the DNA of gametes or embryos (by germline modification). When gene editing is used for germline modification, this is also called *genome editing* because all the cells of the resulting organism have a modified genome.

1.3 First in vitro experiments cause commotion

In 2015 and 2016 Chinese research groups edited the DNA in non-viable human embryos using techniques based on CRISPR to investigate inherited anaemia and HIV resistance. This caused an uproar both within and outside the scientific community. It raised the issue of the morality of this type of research and the consequences of making changes to the genomes of embryos, both for the individual and for society at large. Many researchers, including the discoverers of the CRISPR system, expressed their concern and called for a moratorium and an international debate on how to proceed in a responsible and ethical manner.^{2,3,4,5,6} In response to this, several international meetings have been held, including the International Summit on Human Gene Editing held in Washington D.C.

Various organisations have issued position statements on the use of CRISPR gene-editing technology for germline modification in research and in clinical applications. The first to issue statements were the International Society for Stem Cell Research (ISSCR), The Hinxton Group and the International Bioethics Committee of UNESCO (IBC), followed by the US National Academy of Sciences, Engineering and Medicine and several other international professional bodies.^{7,8,9,10,11,12} In Europe, the Council of Europe and the European Commission's European Group on Ethics have issued statements on human genome editing.^{13,14,15,16,17} More recently, the European Society of Human genetics (ESHG) and the European Society of Human Reproduction and Embryology (ESHRE)¹⁸ have published a statement, as has the Royal Netherlands Academy of Arts and Sciences (KNAW).¹⁹

All these statements make a distinction between the use of CRISPR technology in somatic cells (gene therapy), in research on in vitro human embryos and in clinical applications of the technology for reproductive purposes (germline modification). Gene therapy applications in somatic cells, in which a specific genetic abnormality in the body cells of a patient is repaired and any genetic modifications made are not passed on to subsequent generations, are not considered to be problematic. Germline modification is more complicated. Almost all the position statements call for a moratorium on the clinical application of germline gene-editing technologies until more is known about the safety and effectiveness of these techniques. They also stress the need for international debate on the ethical, legal and social implications of germline genetic modification. The statements by professional groups emphasise to a greater or lesser extent the importance of in vitro research on human embryos.

Various civil society organisations and non-governmental organisations (NGOs) have also made their views on germline modification known. Some see the new possibilities as

a breakthrough and some patients and would-be parents are hopeful for the future²⁰ others are much more guarded. Yet others believe that human germline modification is ethically unacceptable in whatever form and that research on embryos cannot be justified.^{21,22}

1.4 Scientific, legal and ethical questions

The main question in this discussion is whether or not germline gene-editing technologies such as CRISPR can ever be an acceptable option. This question encapsulates several scientific, legal and ethical issues, some of which can be answered now, but others can only be answered sometime in the future.

If CRISPR gene-editing technology is considered to be potentially acceptable for germline modification, more research will be needed into how it works, how effective it is and the possible risks it entails, and this research will have to be done on human embryos. The question then is whether or not it is acceptable to create human embryos for in vitro research into germline modification.

Should the technology be taken to the next stage (the clinical application of germline modification in embryos), other questions will have to be answered as well, including questions about the potential long-term risks. Do the advantages (such as the prevention of genetic diseases) outweigh these risks? And what does germline modification add to existing alternatives? Which disorders may this technique be used to treat, and who should decide that?^{23,24,25} What are the dividing lines between prevention, treatment and human enhancement, and for whom should the technology be made accessible and affordable?²¹ CRISPR and other gene-editing techniques are evolving rapidly, stretching the legal framework to the limit and stirring up the underlying ethical dialogue.

1.5 Legislation and regulations under pressure internationally

At the start of 2016 reports appeared of research in which CRISPR gene-editing technology was used in vitro on non-viable human embryos.^{26,27} Around the same time in the United Kingdom a licence was given to create and modify human embryos for research into the causes of miscarriages.^{28,29} Sweden and Japan have also given permission for experiments on human embryos with modified DNA.^{30,31} These scientists are carrying out research into genetic disorders and fertility problems and see CRISPR gene-editing technology as a suitable tool for this.

At the moment, most European countries prohibit clinical applications of germline modification involving human embryos, and many other countries in the rest of the world have legislation prohibiting germline modification. The United Kingdom is so far the only Euro-

pean country that, in theory, can permit clinical applications of germline modification under certain conditions. Outside Europe this is also possible in the United States. As mentioned above, the pressure to change this situation is mounting as patient groups lobby governments and scientists to make new treatments and reproductive techniques available as soon as possible and to minimise legal and regulatory restrictions on their use.^{32,33}

Both the UK and the US have set up major projects to steer developments in germline modification.^b In February 2017 the US National Academy of Sciences published a report in which it concluded that human germline modification should not be prohibited. It argued that clinical trials with germline modification for medical purposes should be possible within a robust and effective regulatory framework and subject to strict conditions.

Recent developments and discussions indicate that opinions are changing within both the scientific and civil society communities, although there are still many uncertainties surrounding the technical and ethical implications of using gene-editing techniques for germline modification.

1.6 Key questions in this report

This joint report by the Health Council of the Netherlands and the Netherlands Commission on Genetic Modification (COGEM) provides information and analysis to assist the Dutch government in deciding on its position in the international debate on germline modification in human embryos. It is also intended to facilitate this debate.

The report addresses two key questions:

1. What parts of the current normative (legal and ethical) framework are under pressure from developments in the application of gene-editing technologies for making targeted alterations in the genome of embryos, and what are the main ethical and legal issues involved?
2. What questions does this raise for the government, the public, researchers and the medical professions concerned, and what advice can they be given?

1.7 Preparation of the report

This report is a joint publication by the Health Council of the Netherlands and COGEM. In response to international trends, they held the international symposium 'Genome on

^b The Nuffield Council on Bioethics (UK) has investigated the impact of genome editing in agricultural (plants), veterinary (animals) and medical (humans) applications and has developed a set of ethical guidelines for the use of genome editing in humans (see <http://nuffieldbioethics.org/project/genome-editing>). The human gene-editing initiative by the US Academy of Sciences is investigating the scientific possibilities and clinical, ethical and social implications of human gene editing (see <http://www.nationalacademies.org/gene-editing>).

Demand? Exploring the implications of human genome editing’ in November 2015 to identify and describe the technical and ethical consequences of human genome editing. The findings of the symposium have been incorporated in this report. Following further literature research and interviews with external experts, this report was prepared by members of the Standing Committee on Ethics & Law of the Health Council of the Netherlands and the COGEM Subcommittee on Ethics and Societal Aspects. The report was then reviewed and adopted by the Health Council of the Netherlands and COGEM.

In view of the different statutory tasks of COGEM^c and the Health Council,^d the report serves two purposes: to draw attention to the emerging issues and to make recommendations. The trend monitoring sections of the report are presented on behalf of both advisory bodies. Any recommendations put forward in the report are solely on behalf of the Health Council.

1.8 Structure of the report

The report is structured around three main topics:

3. the scientific and technical developments (is germline modification technically possible?);
4. the legislative framework in the Netherlands (is germline modification of human embryos permitted?);
5. the ethical framework (is germline modification of human embryos desirable and morally acceptable?).

Chapter 2 explains what germline genetic modification is in more depth and examines the possibilities and limitations of the application of CRISPR technology. The chapter also describes the scientific and technical problems that need to be resolved before these and other gene-editing techniques can be used in clinical applications.

Chapter 3 outlines Dutch legislation relevant to making targeted alterations in the genome of embryos. This includes legislation on research involving human embryos as well as legislation relevant to human germline modification.

Chapter 4 is about the ethical aspects of scientific research involving embryos and germline modification of human embryos, and the social context in which these issues are considered.

c The statutory tasks of COGEM (Environmental Management Act): 1) giving the government solicited and unsolicited advice on the possible risks to human health and the environment of the production and use of genetically modified organisms (GMOs); 2) giving the government solicited and unsolicited information on the ethical and societal aspects of genetic modification.

d The statutory tasks of the Health Council of the Netherlands (Health Act): giving the government solicited and unsolicited advice on public health issues and health research. In addition, the Health Council of the Netherlands has a monitoring role and may also issue unsolicited advice.

The analyses in Chapters 2, 3 and 4 reveal whether, how and where the technical developments are stretching the legal and ethical framework for germline modification in embryos. The specific questions this raises for stakeholders and interested parties (such as people who want to have children, patients with a genetic disorder and their parents, patient groups, healthcare institutions, doctors, scientists, NGOs, industry and government) are set out in Chapter 5.

Finally, in Chapter 6, in response to these questions, COGEM and the Health Council highlight the relevant issues and trends and the Health Council advises on the policy agenda for the future.

2. Germline modification: applications, limitations and issues

This chapter discusses the possibilities and limitations of altering the genome (the DNA) in human embryos (from now on referred to as germline modification) or in cells involved in reproduction (sperm and ova), focusing on the use of the new gene-editing technology CRISPR for germline modification. The CRISPR system can be used in various ways (section 2.3).

The CRISPR gene-editing technology has the potential to repair certain genetic disorders, but the possibilities are not unlimited. Moreover, it is not always possible to make a clear distinction between a healthy and a defective gene and this has consequences for the discussion about the dividing lines between prevention, treatment and human enhancement (section 2.4). Germline modification would appear to be technically most suitable for repairing single-gene (monogenic) disorders with a Mendelian inheritance pattern. The possibilities for repairing more complex, polygenic and multifactorial disorders and for human enhancement lie far in the future (section 2.5).

Various other scientific issues also have to be resolved, such as the safety of gene-editing techniques, the representativeness of experiments on laboratory animals for humans, the use of surplus human embryos and measuring long-term effects (section 2.6)

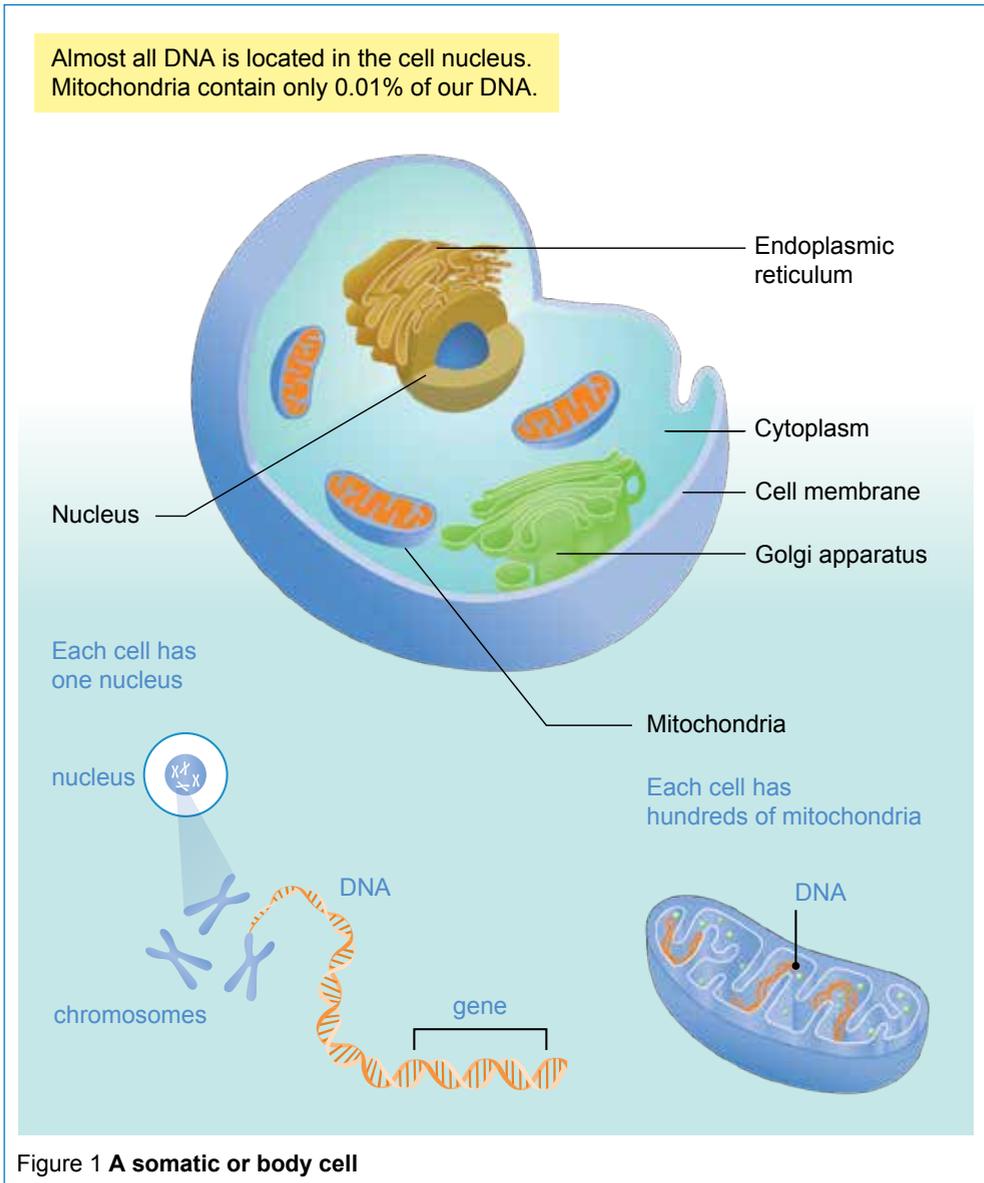
Before discussing germline modification, this chapter starts with a brief explanation of the various types of cell in the human body (section 2.1) and an explanation of the difference between the more 'traditional' cell-gene therapy and germline modification (section 2.2).

2.1 Germline cells and somatic cells

All cells in the human body are enclosed by a cell membrane and are filled with a fluid called cytoplasm. In the cytoplasm are the nucleus and various complex structures, including mitochondria (see Figure 1). The mitochondria are responsible for generating the energy needed by the cell. Although the mitochondria contain just a fraction of all the DNA in the cell, genetic errors in the mitochondrial DNA can have major consequences and cause serious diseases (e.g. Leigh syndrome, Kearns-Sayre syndrome and Alpers-Huttenlocher syndrome).

The cells in the human body can be divided into two types: somatic cells and germline cells. The difference between the two is the ability or not to pass on DNA to the next

generation. Somatic cells (such as the cells in the muscles, organs, brain and bones) are so specialised that they cannot develop into a new individual. This requires cells that are still able to differentiate into all types of body cells. Germline cells are able to do this. The human germline includes the stem cells in the young embryo (totipotent and pluripotent cells), the stem cells for gametes and the gametes themselves (sperm and eggs).



2.2 Germline modification versus somatic cell therapy

There are two ways in which the human genome can be modified: somatic cell-gene therapy and germline genetic modification. In somatic cell-gene therapy, body cells are removed from the patient and later returned to the body after the DNA has been modified (see Figure 2). These cells may be from different tissues, such as cells from the immune system (T cells) or liver cells.

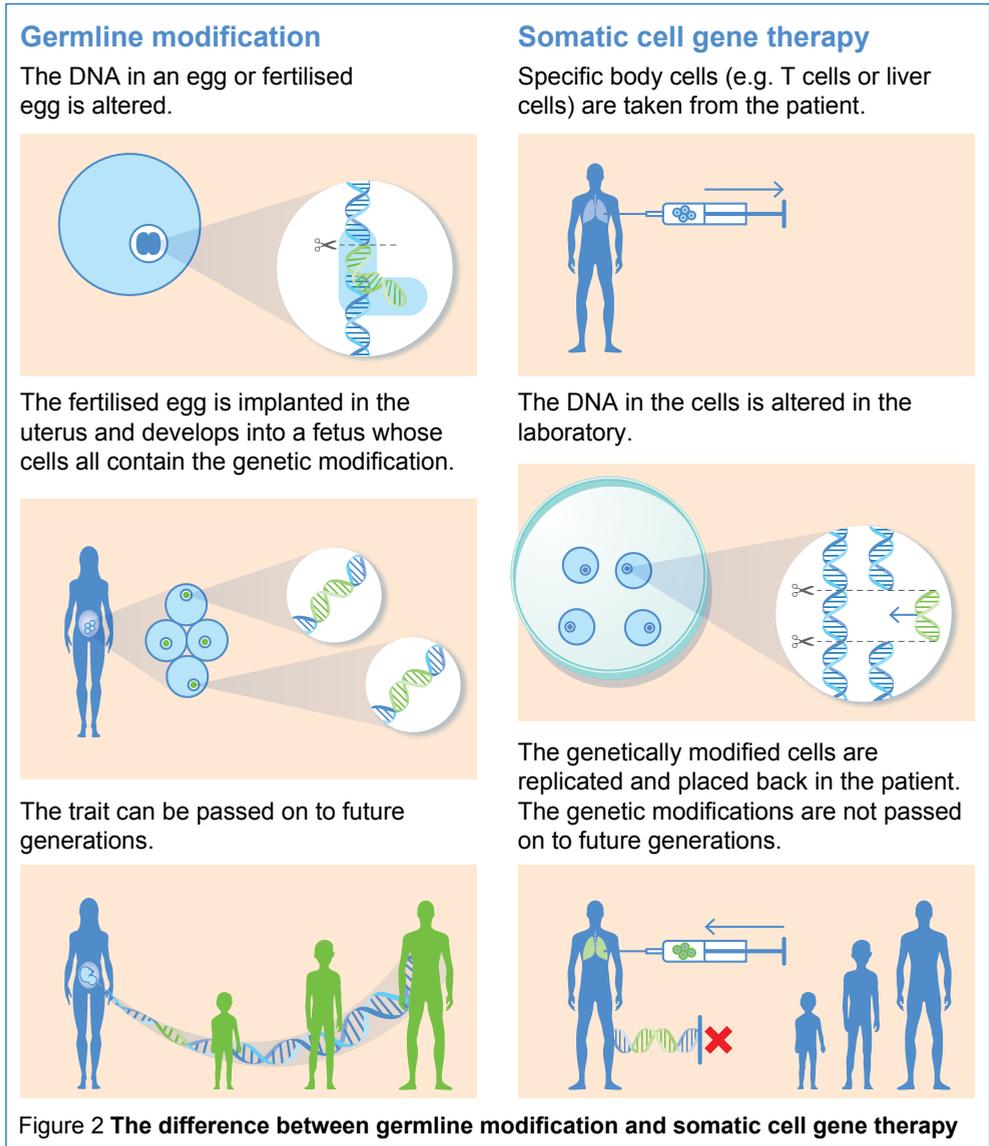


Figure 2 The difference between germline modification and somatic cell gene therapy

The alterations to the DNA are made indirectly by a vector (an adapted virus) or directly by introducing 'naked DNA'. A virus can also be inserted into the patient to make genetic modifications of the DNA in certain cells (gene therapy). These types of therapies fall under the regulations on genetically modified organisms and their use must be authorised (see text box).

Somatic cell-gene therapy and the GMO legislation

Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms defines a GMO as 'an organism, with the exception of human beings, in which the DNA has been altered in a way that does not occur naturally by mating and/or natural recombination'. According to EU rules, people cannot be genetically modified organisms. However, somatic cell-gene therapies in which cells are removed from the human body, modified outside the body using 'naked DNA' and then returned to the body do fall under the GMO legislation and may be permitted under certain conditions.

This type of gene therapy has been improved and refined by the use of CRISPR technology as a tool for making highly accurate alterations to DNA. For some years clinical studies have been carried out using zinc finger nuclease (ZFN) and transcription activator-like effector nucleases (TALENs) gene-editing techniques, and the first clinical trials for somatic cell-gene therapy using CRISPR have been announced and approved.^{34,35} In somatic cell-gene therapy the alterations made to the DNA are not passed on to future generations.

This report concentrates on the other application: *germline modification*, also called *human genome editing*. In this application the genetic modifications are passed on to future generations. The genetic modifications are made in reproductive cells or in embryos at an early stage of development (germline cells).

2.3 Modifying the DNA in the germline

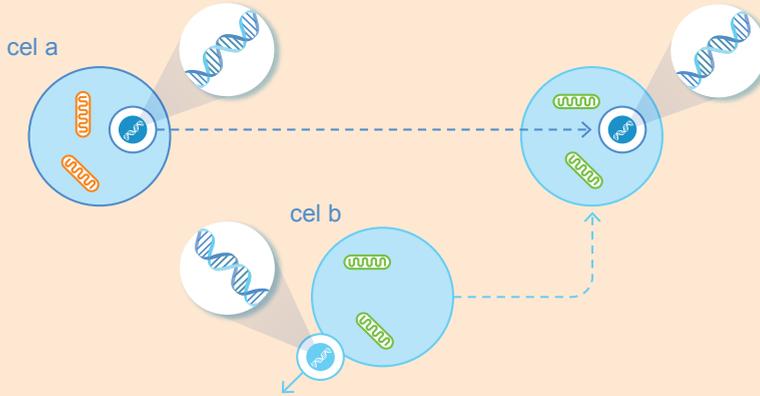
Germline cells can be modified in various ways. A distinction can be made between the use of donor material (mitochondrial replacement therapy and testicular stem cell transplantation) and the direct modification of the genome without the use of donor material, or genome editing (see Figure 3).³⁶ A distinction can also be made between modifying mitochondrial DNA and modifying the DNA in the cell nucleus.

Mitochondrial replacement therapy

Replacing defective mitochondria with healthy ones can prevent the onset of serious disorders or diseases. As each cell contains hundreds of mitochondria it makes little sense to try

Cell nucleus transplantation

The nucleus of an egg or fertilised egg with defective mitochondrial DNA is transferred to a donor egg or fertilised donor egg from which the nucleus has been removed.



Modification of the cell nucleus (germline modification)

The DNA in the nucleus of a sperm or egg is altered using CRISPR-Cas or another gene-editing technique.

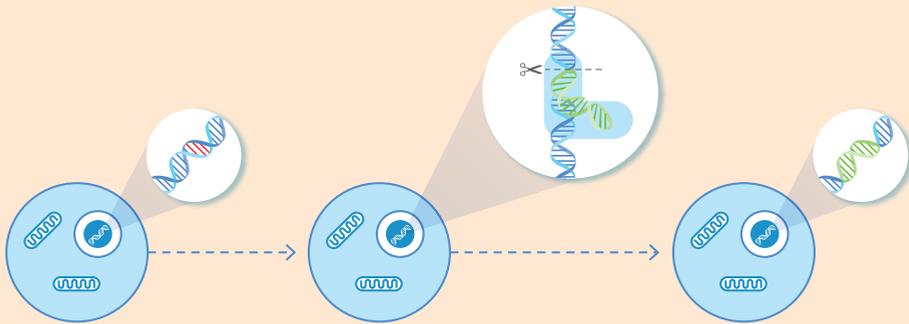


Figure 3 Two ways of altering the DNA in gametes

to repair the mitochondrial DNA itself. Three methods have been developed for mitochondrial replacement therapy and each makes use of donor material:

1. *Ooplasmic transfer*: the in vitro injection of cytoplasm from a 'healthy' donor egg (containing 'healthy' mitochondria) into an egg with defective mitochondria. The modified egg is then fertilised with a sperm and transferred to the uterus. This egg (or embryo) contains both healthy and defective mitochondria.
2. *Maternal spindle transfer*: the in vitro transfer of the nucleus of an egg with defective mitochondria into a healthy donor egg from which the nucleus has been removed. The modified egg is then fertilised and transferred to the uterus.

3. *Pronuclear transfer*: in this technique the egg is transplanted after fertilisation; the nucleus of a fertilised egg containing defective mitochondria is injected in vitro into a donor egg from which the nucleus has been removed.³⁷

Use of mitochondrial replacement therapy in practice

Ooplasmic transfer (or cytoplasmic transplantation) was first done in 1997. Worldwide, about 30 children conceived using this technique have been born.^{38,39} However, various complications may arise as a result of heteroplasmy (having both healthy and defective mitochondria present in cells), which may lead to abnormalities.⁴⁰ This technique is offered by IVF clinics in some European countries.^{41,42,43}

Maternal spindle transfer has been successfully carried out in monkeys and in vitro in human cells, with apparently normal development of the resulting embryo.^{44,45} In September 2016 it was announced that the technique had been successfully used to prevent the transmission of Leigh syndrome (a serious metabolic disease). A Jordanian couple called on the assistance of Chinese and American specialists, who for legal reasons carried out the procedure in Mexico.⁴⁶

Pronuclear transfer was first carried out in 2003 in China, but as a result of various complications none of the transferred embryos reached full term.^{47,48,49,50} This technique has since been developed further and is seen as the best method for preventing mitochondrial diseases. Pronuclear transfer is not used in the Netherlands because scientific research into the feasibility, effectiveness and safety of the technique is not permitted.⁵¹ In England a law was amended in 2015 to make it legal to offer pronuclear transfer (and also maternal spindle transfer) in IVF clinics.⁵² In 2016 it became clear that pronuclear transfer had already been carried out in Ukraine to treat fertility problems.^{53,54,55}

Testicular stem cell transplantation

Germline cells can also be replaced by means of testicular stem cell transplantation – transplantation of the stem cells that produce sperm. These may be from a donor (if there are genetic fertility problems) or from the patient himself (from whom they are removed before a drastic medical treatment, for example for cancer, after which they are re-implanted).⁵⁶ Research on this technique is also being carried out in the Netherlands.⁵⁷ In principle the technique could also be used to modify the DNA in the testicular stem cells so that they produce modified sperm cells, thus preventing the transmission of certain genetic disorders (such as Swyer syndrome, in which patients are externally female but have male chromosomes). This technique has been successfully used on mice.⁵⁸ In addition, in vitro research has been done on the possibilities for its use in human cells.⁵⁶

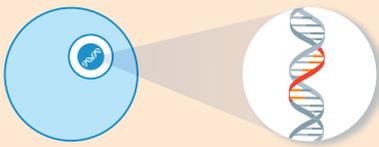
Modification of the cell nucleus (germline modification)

In the alternative method for altering germline cells – modification of the cell nucleus, or germline modification – alterations are made directly to the DNA of germline cells without the use of donor material. As mentioned above, various gene-editing techniques are available to do this, such as ZFN, TALENs and CRISPR. These techniques have already been extensively used to make modifications in germline cells of animals (both in vitro and in vivo) but only in a very few cases in human embryos (only in vitro). The technology based on CRISPR is considered to be the most promising technique because of its broad applicability, efficiency and accuracy.^{59,60,61,62} This technology is described briefly below.

CRISPR-Cas can be thought of as a biological version of the ‘search and replace’ function in a word processor. It can be used to alter the DNA by cutting, replacing or adding pieces of genetic code.

An example of how the technique works

The genetic material in a cell (the DNA) contains an undesirable mutation.



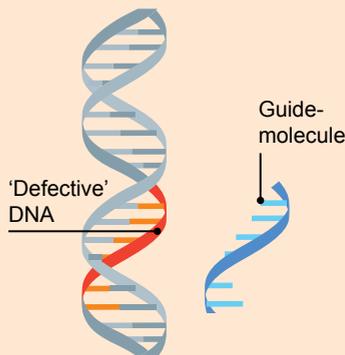
The ‘defective’ DNA sequence can be changed with the help of a protein complex consisting of:

- a ‘guide molecule’ (CRISPR)
- a ‘DNA-cutting’ protein (Cas)
- a piece of DNA without the mutation



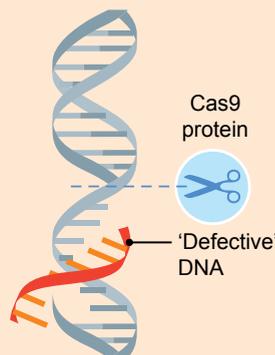
1

A specially designed guide molecule ‘reads’ the DNA in a cell until it finds a piece of ‘defective’ DNA that matches the sequence implanted in the guide molecule.



2

The Cas protein then cuts out this piece of DNA (deletion).



3

The deleted piece of DNA can now be replaced with a DNA sequence that does not have the undesirable mutation.

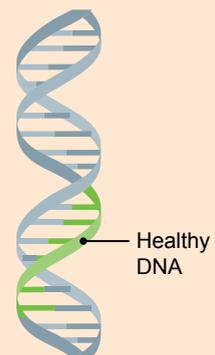


Figure 4 Example: How does CRISPR-Cas work?

CRISPRs are short segments of repetitive base sequences in the DNA of bacteria. These patterns were discovered in 1987 by Japanese scientists. Later, other scientists saw that the repetitive DNA patterns play a role in bacterial defence systems. Bacteria have developed a special technique to defend themselves against viruses in which they build a piece of the virus into their own DNA. This enables them to recognise the virus when it next attacks and inactivate it. After RNA molecules have detected the viral DNA, special enzymes (such as the Cas9 protein) cut the virus DNA. Other enzymes have now been discovered that can do this as well (such as Cpf1).⁶³

In recent years it has become clear that this defence mechanism can be used to alter the genetic code in other living organisms. The technique makes it possible to cut a strand of DNA at a precise locus. Using CRISPR, therefore, it is possible to make specific changes in the genome of animals, plants and microorganisms by cutting out and adding DNA (see Figure 4).

2.4 Diagnosing genetic disorders

The possibilities of germline modification using the CRISPR technology are not endless. Genetic factors play an important role, but not the only role, in the development of various diseases and disorders. In some cases environmental and nutritional factors have an influence. Technically, the most likely candidates for germline modification are monogenic (single-gene) disorders with a Mendelian inheritance pattern, which are caused for the most part by a mutation in a single gene. To repair the genetic causes of these diseases it is only necessary to make an alteration at one place in the gene.

Each year about 7.9 million children (6% of all births worldwide) are born with a genetic disorder.⁶⁴ The seriousness of the symptoms of genetic disorders vary, as do the possibilities for prevention and treatment. An estimated 6,000 to 7,000 genetic diseases are caused by a mutation in a single gene (monogenic disorders).^{65,66} Other estimates vary considerably, from 7,000 to 15,000.⁶⁷ About half of these disorders (approx. 3,500) have been identified, which means that the error in the DNA that correlates with a specific illness or clinical presentation has been found.⁶⁵ For a long time many disorders have been difficult to diagnose because they are associated with a wide range of symptoms, such as developmental delays, motor dysfunction, infections, heart and kidney problems and epileptic fits, and it was hard to tell whether or not the symptoms were related and indicative of a specific disorder.

Next generation sequencing (NGS), which makes it possible to map large parts of the complete genetic code of an individual, is continuing to make a valuable contribution to the diagnosis of rare genetic disorders. However, there are still many scientific and technical aspects of the diagnosis and cause of genetic disorders that remain to be resolved.

Unresolved problems with the diagnosis of genetic disorders

Tracking down genetic defects in the DNA is one thing, but linking them to a specific clinical presentation (i.e. making a diagnosis) is another. For many disorders, the relation between the genetic defect (genotype) and its physical expression (phenotype) has not yet been clarified. An example is Pompe disease, a genetic metabolic disorder. Pompe patients with the same genotype (the same genetic disorder) display a wide variety of physical characteristics.⁶⁸ The opposite situation is also found, for example in cystic fibrosis, for which 1,500 mutations are known, all of which give rise to a similar clinical presentation.⁶⁹ A common problem in clinical practice is that a defect is found in a gene without any clear evidence that it explains the symptoms displayed by the patient.

Another problem that has not yet been resolved is the role and function of the large amounts of non-coding DNA (sequences which do not code for genes).⁷⁰ The human genome in the cell nucleus consists of about 3 billion base pairs and according to the latest estimates contains about 19,000 protein-coding genes. This is just a small percentage of the total DNA; more than 95% of the human genome is currently considered to be non-coding 'junk DNA', including repetitions and evolutionary artefacts. However, there are growing indications that parts of these sequences do indeed have an important function.⁷¹

2.5 Technical possibilities and limitations of germline modification

2.5.1 Modifying genes

Some genetic disorders are caused by one or more defects in a particular gene. If the defective DNA code can be removed with precision and replaced by the correct code, it is theoretically possible to treat the disorder by germline editing techniques. Scientific research indicates that with CRISPR gene-editing technology it is in principle possible to modify DNA with absolute precision, down to the letter.^e An example of a heritable disorder caused by a single genetic defect (a point mutation) is sickle-cell anaemia (see text box).

e Deoxyribonucleic acid (DNA) consists of nucleotides containing one of four nucleobases: adenine, thymine, guanine and cytosine, abbreviated to the letters A, T, G and C. The order of these bases codes for specific amino acids which go to make up the proteins that take care of our bodily functions.

Sickle-cell anaemia: an example of a disease caused by a point mutation

Sickle-cell anaemia is a blood disease caused by an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells. It leads to chronic anaemia and various other complications, such as an increased chance of infections, thrombosis and organ damage. The life expectancy of patients with sickle-cell anaemia in the developed world is 46 years.

Sickle-cell anaemia is caused by a point mutation in the beta-globin gene on chromosome 11 in which the adenine (A) base is replaced by thymine (T), resulting in the synthesis of the amino acid valine instead of glutamic acid.⁷² This in turn leads to an abnormal type of haemoglobin which spontaneously forms insoluble polymers, giving the cells a rigid sickle-like shape. The cells either stick together to form clumps or are easily broken down. Sickle-cell anaemia is a genetic disease with an autosomal recessive pattern of inheritance. 'Autosomal' means that the defective genes are not found on the sex chromosomes (X or Y), so men and women have the same chance of contracting the disease. 'Recessive' means that both parents must be carriers of the sickle-cell anaemia mutation to pass the disease on to their children. Children of parents that are both carriers have a 1 in 4 chance of developing sickle-cell anaemia.

Sickle-cell anaemia is incurable. Treatment aims to ease the symptoms (pain management) and prevent or control complications, for example by fluid therapy, antibiotics and blood transfusions. Gene therapies are also being developed to treat the disease.^{73,74} A recent paper gives cause for hope that a somatic cell-gene therapy may be developed for sickle-cell anaemia. The researchers used CRISPR technology to correct the point mutation in the blood stem cells in human cells and in mouse models.⁷⁵ In the short term it may be possible to pursue another strategy in which the part of the gene that synthesises the beta-globin chain in haemoglobin is cut out. The body will then fall back on making the type of haemoglobin that is made before birth (fetal haemoglobin).⁷⁶ People who only make fetal haemoglobin do not have any symptoms of the disease.

Other genetic disorders caused by point mutations include glaucoma, colour blindness, Tay-Sachs disease and cystic fibrosis.

2.5.2 Removing defective genes

Gene-editing techniques can be used to remove whole genes or parts of genes relatively simply and efficiently. An example of a disease which can be prevented by removing genetic information is Huntington's disease, which is caused by an abnormal number of repeats of a specific DNA sequence.

Huntington's disease: an example of a disease caused by repeated DNA sequences

Huntington's disease is a genetic disease caused by the slow, progressive death of nerve cells in certain parts of the brain.⁷⁷ The most common signs of the disease are involuntary movements, loss of cognitive abilities and a range of psychiatric symptoms. The disease is caused by a defective gene on the fourth chromosome, which produces an altered or defective protein. The gene contains an abnormally long trinucleotide repeat (CAG) at chromosome locus 4p16.3. The number of CAG repeats is inversely correlated with the age of onset of the disease.

The first symptoms usually become noticeable between the ages of 35 and 45, but there is also a juvenile form of the disease that begins during the teenage years.⁷⁸ Most patients die on average sixteen years after the onset of symptoms. Huntington's disease is an autosomal dominant genetic disorder. This means that every child that has one parent with Huntington's disease has a 50% chance of getting the disease. If a parent is homozygous for Huntington's (i.e. carries two identical copies of the gene, which is rare), all offspring will inherit the disease.

The symptoms of Huntington's disease can be treated to reduce their severity, but there is no cure. Several biotechnology companies are working to develop a gene therapy for Huntington's that uses the ZFN and CRISPR technologies to disrupt expression of the CAG repeats in the brain cells and so delay the progression of the disease.^{79,80} This has proved to be effective in mice.⁸¹ The disadvantage of the gene therapy approach is that it is almost impossible to treat all the millions of brain cells in a patient. However, it may not actually be necessary to do that. Experience with a number of different conditions caused by genetic disorders is that partial correction, from 40% to just 10%, can be sufficient to significantly reduce or eradicate the effects in a laboratory animal or cultured human cells.⁸² CRISPR gene-editing technology could be used to remove some or all of the CAG repeats in the germline, which could result in the disease not being expressed, or only in a milder form, or at a later age. Moreover, the repaired gene could then be passed on to the patient's children and future generations. This approach has been investigated in mice and the researchers say the results have been promising.⁷⁹

Besides Huntington's disease, various other genetic disorders are caused by an abnormal number of repeats of a specific DNA sequence. They are called triplet repeat disorders⁸³ and include spinocerebellar ataxia, fragile X syndrome, spinal and bulbar muscular atrophy, and myotonic dystrophy.

2.5.3 Gene insertion

Some genetic disorders are caused by the absence of a gene or the absence of part of a gene or chromosome, which results in certain proteins being synthesised incorrectly or not at all.

Gene-editing technology can be used to insert an additional sequence of DNA at a specific locus in the genome. However, the longer the sequence of base pairs, the more difficult the insertion becomes. An example of a genetic disease caused by the deletion of a DNA sequence is Duchenne muscular dystrophy (DMD).

Duchenne muscular dystrophy: an example of a disease caused by the absence of a gene

Duchenne muscular dystrophy (DMD) is an inherited form of muscular dystrophy caused by the absence of the protein dystrophin. The lack of this protein leads to progressive muscle degeneration and weakness, eventually affecting the heart and respiratory muscles. Most patients are confined to a wheelchair by the time they are twelve and rarely live longer than thirty years.⁸⁴ DMD is an X-linked recessive disorder and primarily affects men, because they have only one X chromosome. Boys have a 50% chance of inheriting the disease from their mother if she is a carrier.

The defect in the production of dystrophin can be caused by various mutations (deletions) in the dystrophin gene at locus Xp21 on the X chromosome.⁸⁵ Duchenne deletions are frameshift mutations that cause a shift in the reading frame in the gene (as if the spaces between the words in a sentence are randomly inserted). As a result no correct protein can be synthesised from the gene.

DMD is incurable. Research into the disease currently focuses, among other things, on gene therapy using exon skipping^f to make the deletion larger so that it falls within one of the reading frames. The protein synthesised by the sequence of genetic code is then truncated – a bit of the ‘text’ is missing, but the beginning and the end are intact and it is still functional. This form of deletion is associated with Becker’s muscular dystrophy, which has much less serious symptoms than DMD.⁸⁶

Potential germline editing treatments for DMD have been investigated in mice, with highly variable results. In some cases the defective gene was hardly repaired at all and in other cases it was fully repaired.⁸⁷ The possibilities for repairing DNA with missing sequences using gene-editing techniques are limited by the maximum size of insertions. This means that disorders that are caused by big deletions of pieces of genes or chromosomes, such as DMD, cannot always be repaired. With the current techniques it is not possible to insert a full dystrophin gene into the genome.

Other genetic disorders that are caused by the deletion of a gene or part of a gene or chromosome include Cri du Chat syndrome (5p deletion), velo-cardio-facial syndrome (22q11.2 deletion), Wolf-Hirschhorn syndrome and Jacobsen syndrome.⁸⁸

^f DNA consists of sections that code for proteins (exons) and sections that do not code for any specific proteins (introns). Exon skipping is when pieces of coding DNA that contain errors are passed over.

2.5.4 Polygenic disorders and enhancement

Polygenic disorders are caused by a complex of mutations in multiple genes (sometimes in combination with environmental factors). Editing the germline to prevent such disorders will be a highly complex, if not impossible, operation.⁸⁹ This is especially the case for genetic defects that present a risk in combination with environmental factors or lifestyles, such as heart diseases, certain forms of breast cancer, Alzheimer's disease, arthritis and diabetes.

Besides repairing genetic disorders, germline genetic modification could also be used for human enhancement purposes, such as providing resistance to diseases and preventing food allergies or intolerances (e.g. gluten and lactose). However, these more complex disorders and characteristics are not necessarily the result of genetic defects.

For example, 1% of the American population have a mutation in the *CCR5* gene and research has shown that these people are resistant to infection with the R5 variant of HIV. This suggests that modifying the *CCR5* gene in the immune cells of a patient would be an effective treatment for this HIV variant, and also that the germline could be edited to confer 'resistance' to this HIV variant from birth. Other examples of known risk factors are the *APOE* gene, which increases the risk of Alzheimer's and heart disease, and the *PCSK9* gene, which gives an increased risk of heart failure.

However, a certain genetic make-up may have persisted in the population because it is linked to other functions as well and so modifying genes to reduce the risk of or sensitivity to one disease could raise the risk of other diseases.

The *CCR5* mutation that provides protection against HIV is known to increase susceptibility to the West Nile virus.⁹⁰ Also, the variant of the *APOE* gene that is linked with Alzheimer's is also associated with brain function in young adults. The converse is also possible: a mutation that has undesirable effects can also have a beneficial side-effect. There are indications that people with the Delta F508 mutation that causes cystic fibrosis also have an increased chance of surviving a cholera infection.^{91,92} Some genes are known to have several functions, some beneficial and some harmful to the condition of the organism carrying them. This phenomenon is called antagonistic pleiotropy. Geneticists suspect that this may be the case for an unknown number of other genes as well.⁹³

The possibilities of using germline editing techniques for human enhancement are not limited to disease resistance, but also include more dramatic applications like changing a person's outward appearance, intelligence, sporting performance and lifespan, and also non-human traits such as tolerance of high and low temperatures and heightened senses. Many of these enhancements would involve modifying complex polygenic traits which, in principle, cause no adverse effects or diseases. Opinions are divided about the desirability of modifying these types of genetic traits. For example, to create a top athlete, genetic modifications could be made to enhance muscle development and phy-

sique, while overstimulation of the erythropoietin gene would lead to high haemoglobin levels in the blood, thus improving oxygen transport capacity.⁹⁰ But top athletes possess many more abilities that all add up to give them the edge they have over others, such as eye-hand coordination, willpower, discipline, performing under pressure and intelligence. Much less is known about these characteristics.⁹⁴ Environmental factors and nutrition also have an important effect on sporting performance. Increasing intelligence would also be a highly complex business. Although research indicates that certain genes can be associated with intelligence,⁹⁵ this trait may be influenced by hundreds of genetic and non-genetic factors.⁹⁶ Scientists are therefore sceptical about the possibilities of using germline editing techniques to improve intelligence or other human characteristics.^{89,97}

2.6 Scientific issues surrounding germline genetic modification

Besides the technical aspects of germline modification discussed above, there are also scientific issues that limit the possibilities of germline modification, at least for the time being. These are discussed below.

2.6.1 Reliability and safety

The issue of whether or not gene editing works properly and is safe as a method for germline modification can be answered by examining its:

- *effectiveness* (will the intended genetic modification be made?);
- *accuracy* (will any unintended (off-target) genetic modifications be made?);
- *efficiency* (will the intended modification be made correctly in all cells and what is the success rate – how many embryos on average would be needed to carry out a successful germline modification?).

Research into improving the effectiveness, accuracy and efficiency of the CRISPR gene-editing system is ongoing. At the start of 2016 a research group in the US claimed to have improved the system to such an extent that off-target effects in human cells could no longer be detected.⁹⁸ However, research into cell lines or tissues does not always accurately reflect how the technique works in living organisms.

Genome editing has already been successfully used to make germline genetic modifications in animals (both in vitro and in vivo), but only in a very few cases in human embryos (only in vitro). The first modifications made to the DNA in human embryos using the CRISPR technology show that the technique is not always efficient and accurate and that it can lead to unwanted effects.

Efficiency and accuracy of CRISPR-Cas modifications in human embryos is limited

Early in 2015 Chinese researchers published the results of a study in which they had used CRISPR technology to modify the genome in human embryos.⁹⁹

Non-viable human embryos were used.⁹ The researchers aimed to modify the gene for beta-thalassemia (a genetic blood disease which leads to chronic anaemia). They reported incomplete editing of the DNA in the cells (mosaicism),^h inaccurate editing and off-target mutations.ⁱ Of the 86 embryos, 71 survived injection with the CRISPR machinery. Some of these (54) were genetically tested, which revealed that the DNA in 28 of them had indeed been cut, but the corrected gene had been inserted in only a fraction of these. The researchers concluded that the effectiveness and efficiency of the technique is still too limited to permit its use on normal embryos.

In 2016 a second study was reported in which the CRISPR technology was used on human embryos. The Chinese researchers had used the gene-editing technique to attempt to modify the *CCR5* gene in non-viable embryos. A specific variant of this gene is associated with HIV resistance (see section 2.5.4), but here too the technique proved to be inefficient. Of the 26 embryos treated in the study, just 4 had the intended genetic modification.^{100,27} Moreover, these 4 embryos also exhibited off-target effects and mosaicism. Some researchers think this poor efficiency is partly due to the genetic make-up of the embryos. This can only be verified by carrying out research on human embryos with a normal genetic make-up.

2.6.2 Relevance of laboratory animal research

In recent years the CRISPR technology has been used to edit the genomes of a range of animals, including mice, rats, fish, chickens, pigs, sheep, goats, cows, dogs and monkeys.^{99,101} Medical studies and fundamental research into the function of human genes are often performed on humanised^j mice and rats. These laboratory animals are not only easy to keep and breed, but they can also relatively easily be adapted to display genetic similarities to humans, both in the functions of certain genes and by possessing genes associated with diseases. Genetically modified mice are therefore commonly used as disease models to investigate diseases and develop treatments for them.

g These were tripronuclear embryos, which are embryos that develop from ova that are fertilised by two sperm cells at the same time. These embryos therefore contain three sets of chromosomes and are not viable.

h Mosaicism is when some cells have been modified and some have not.

i Off-target mutations are mutations made unintentionally in DNA sequences outside the genes being targeted. They are caused when the CRISPR system recognises a sequence of DNA similar but different to the one it was designed for and makes changes to this section.

j Humanised laboratory animals have been genetically modified to express human genes associated with certain traits or illnesses.

However, once the step is made to clinical studies on humans, often there are big differences in the effectiveness of the treatments.¹⁰² There are also considerable differences between animal and human embryos regarding the fundamental embryological mechanisms, the timing of specific developments, the formation and structuring of tissues and the general morphology of the embryo. For example, the mice embryonic genome is activated in the two-cell stage about one day after fertilisation, whereas in human embryos genomic activation occurs at the eight-cell stage, after about three days. It has also been shown that essential regulatory genes, such as *PAX6* for neural development and *SOX17* for germline development, function differently in mice and humans.^{103,104,105} These differences indicate that various assumptions about developmental stages based on ‘knockout’ research in mice (in which certain genes are inactivated) may not be representative of human biology.

Other animals, such as monkeys and apes, display many more genetic similarities with humans: the genome of the rhesus monkey is 98% the same as the human genome and the chimpanzee genome is even more similar. Research on these laboratory animals is therefore generally more representative for the human situation. In 2014 various research groups announced they wanted to make more genetically modified monkeys for use as model systems for research into human diseases.¹⁰⁶ But these also have their limitations. In 2016 a Chinese research group published the results of a study in which genetically modified monkeys were created that display autistic traits.¹⁰⁷ The study was criticised because of scientific doubts about the representativeness of using animal models such as monkeys for research into psychological disorders.¹⁰⁸

This issue of representativeness raises questions about the justification for using animals for such studies. Nevertheless, studies on animal models can throw up important indicators of the safety and efficiency of using germline gene-editing techniques, and if problems are found, such as off-target effects, these will first have to be solved before any preclinical studies can be performed on human embryos.

In many countries there are also ethical objections to the use of monkeys and apes for medical research. For this reason, EU legislation is based on the principle that experiments with monkeys and apes are only permitted if there are no alternatives.¹⁰⁹ In the Netherlands, since 2002 research on monkeys and apes has been permitted only for a restricted number of studies for which there is no alternative (Experiments on Animals Act, Article 10, paragraph 2) and only on non-anthropoid primates such as rhesus monkeys, crab-eating macaques and marmosets. Tests on apes, such as chimpanzees, are prohibited.¹¹⁰

2.6.3 Restrictions on research involving human embryos

Research on laboratory animals, even on apes (hominoids), will probably eventually prove not to be representative enough for the human situation. It will therefore be necessary to carry out research on human embryos to investigate the mechanism and safety of germline gene-editing techniques. However, the scope and nature of such

research is bound by legal and scientific restrictions. The legal restrictions on embryo research are described in detail in Chapter 3; here we look at the scientific and technical restrictions.

In the Netherlands research is currently permitted, under certain conditions, only on surplus embryos: unused embryos from assisted reproduction treatments, which would otherwise be destroyed. Surplus embryos can be divided into various categories: healthy viable embryos; unhealthy or affected but viable embryos; and non-viable embryos. Not all categories are suitable for scientific research. The number of available surplus human embryos is therefore limited.

Another restriction on using surplus embryos in scientific research is that they are already six to eight days old when they become available, which obviously makes it impossible to study the initial stages of development. Moreover, gene-editing techniques require every cell in the embryo to be genetically modified, which means that the chance of mosaicism increases the longer the embryo has developed and the more cells the embryo consists of.

A third technical restriction on research involving human embryos is the internationally agreed stage of development beyond which research is no longer permitted: fourteen days. The fourteen day limit is in fact a theoretical maximum, because culturing embryos has proved to be extremely difficult in practice. However, in 2016 for the first time human embryos were successfully cultured in vitro for thirteen days.¹¹¹

2.6.4 Measuring long-term effects in clinical applications

Various researchers have successfully used CRISPR gene-editing technology in germline cells of animal embryos. Genetic modifications made in a fertilised egg or an embryo at an early stage of development are passed on to every cell in the body, which means that the effects in a fully grown organism are irreversible. However, it is theoretically possible to reverse the genetic modifications in subsequent generations by making a new germline modification. The effects of germline modifications on later generations need further investigation, which raises the question of how to measure long-term effects.

The long-term effects and consequences of germline gene editing in humans can only be investigated when modified human embryos are transferred to the uterus, are born and grow into adults. At an early stage of development – and even before birth – it is possible with whole genome sequencing to map an individual's complete DNA to check for any off-target effects. However, it is questionable whether it would be possible to distinguish between effects caused by gene editing and effects caused by other mutations, which occur spontaneously throughout growth, development and the process of cell renewal in the human body. Some of these mutations are repaired, but others remain and some of those have an effect (either beneficial or adverse). An important question in the discussion is whether adverse effects are reversible or not.

Some experts are concerned that germline modification will irreversibly change the future human gene pool. Others argue that widespread changes in the germline could be problematic for international or global genetic diversity, but that the impact of less drastic changes in small populations (such as groups of patients with a rare genetic disease) would be much smaller. Each step in this process involves many variables, which makes it difficult to trace any potentially adverse effects back to the germline modification. In short, thought should be given to how the long-term risks to individuals and subsequent generations can be investigated, and to how such risks can be taken into account when making decisions on possible clinical applications.

2.7 Conclusions to Chapter 2

The genetic changes made to gametes by germline editing are irreversible for the resulting individual and are passed on to future generations. In theory, germline modification can be used to prevent genetic disorders in descendants. Gene-editing techniques such as CRISPR can be used to repair some genetic disorders in the embryo.

Besides repairing genetic disorders, germline editing could also be used for human enhancement purposes, such as providing resistance to diseases. However, modifying genes to reduce the risk of or sensitivity to one disease may increase the risk of getting other diseases. Scientists are sceptical about the possibilities of genome editing to improve intelligence or other human characteristics.

The examples given in this chapter suggest that it is not always possible to make a clear distinction between treatment and enhancement, or between a defective and a healthy gene – although clear examples of both can be found. Advances in genome editing techniques will bring these questions to the fore again (see section 4.3.4). At the moment, the greatest potential of germline gene editing is for treating monogenic disorders – genetic diseases caused for the most part by a mutation in a single gene – because changes only have to be made at a single locus in the gene. Scientists believe that germline modification has little chance of success for polygenic disorders (disorders caused by several different genes) and disorders that are not fully heritable.

If germline modification is considered to be a morally acceptable option for preventing genetic diseases from being passed on to future generations, more research will be needed into the mechanism and safety of gene-editing techniques for these applications, including the effectiveness, accuracy and efficiency of the method, for example through laboratory animal research. Such research, however, has its limitations, because laboratory animals such as mice and rats are not fully representative of humans. The use of laboratory animals that are genetically more similar to humans (such as apes) raises ethical objections, and using surplus human embryos for research has its technical limitations.

In short, various scientific and technical issues still have to be resolved to remove or reduce the uncertainties still surrounding the mechanism and safety of germline genome editing.

Moreover, scientific research on laboratory animals and human embryos will never be able to demonstrate with 100% certainty that a specific application of germline modification is effective, accurate and efficient. Only clinical applications will eventually be able to resolve these issues, but this raises the question of when the risks are small enough and the potential benefits great enough to justify taking this step.

3. Legal aspects

This chapter examines the international, European and national legislation regulating the genetic modification of embryos. The discussion focuses on the points on which the Dutch legislation is at odds with (a) the need to do scientific research into germline modification and use this technique in clinical applications, and with (b) international legislation. It looks in turn at the internationally agreed human rights that aim to safeguard human dignity (section 3.1), the international conventions and declarations relating to genetic modification (sections 3.2 and 3.3) and Dutch and EU legislation on embryos (section 3.4).

Culturing embryos for research purposes is not permitted in the Netherlands. However, in 2016 the Minister of Health, Welfare and Sport sent a letter to the Dutch House of Representatives announcing a revision of the Embryo Act making it permissible, under strict conditions, to create embryos for a limited number of research purposes.¹¹²

3.1 Human rights

The purpose of the human rights legislation is to ensure that every person, wherever they are in the world, can live in human dignity. There is no precise definition of human dignity, but it is associated in various contexts with physical and psychological integrity, individual autonomy, material living conditions and equality.¹¹³ Human rights are set down in international conventions and declarations, such as the Universal Declaration of Human Rights (UDHR), the International Covenant on Civil and Political Rights (ICCPR) and the European Convention on Human Rights (ECHR) (formerly the Convention for the Protection of Human Rights and Fundamental Freedoms).

Human rights in national constitutions are called fundamental rights. Human rights and fundamental rights impose negative obligations on states to monitor and protect the fundamental rights of their citizens.¹¹⁴ This means that states must refrain from certain actions which would violate people's rights or freedoms, such as the right to respect for privacy (Article 10 of the Dutch Constitution) and the right to inviolability of a person (Article 11 of the Dutch Constitution), without prejudice to restrictions laid down by or according to laws. Human rights and constitutions also impose positive obligations on states: they are required to take steps to guarantee certain rights and freedoms, including measures to promote the health of the population (Article 22.1 of the Dutch Constitution).

Provisions of treaties or conventions to which the Netherlands is a party and which may be binding on all persons become binding after they have been published (Article 93 of the Dutch Constitution). Moreover, Article 94 of the Dutch Constitution states that when provisions of a treaty or convention are in conflict with national legislation, the latter

do not apply. Provisions of treaties or conventions that are binding on all persons (and have been published) enter into force immediately. Whether or not a provision is binding on everyone depends on the intention of the authors of the treaty or convention (was it their intention that the provision should be directly applicable?) and the content of the provision (is it concrete enough?). If a provision is 'binding on all persons', individuals can appeal directly to the provision, irrespective of the existence of regulations in national law.¹¹⁴

3.2 Conventions and declarations relating to germline modification

There are global and European conventions and declarations relevant to the genetic modification of human cells. In the field of human germline modification there are two key UNESCO declarations: the Universal Declaration on the Human Genome and Human Rights (1997) and the Universal Declaration on Bioethics and Human Rights (2005).

UNESCO declarations on human rights relating to the human genome and bioethics

International Declaration on the Human Genome and Human Rights (1997)

Article 5 (a): Research, treatment or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law.

Article 11: Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to co-operate in identifying such practices and in taking, at national or international level, the measures necessary to ensure that the principles set out in this Declaration are respected.

Universal Declaration on Bioethics and Human Rights (2005)

Article 2: The aims of this Declaration are:

- (a) to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics;
- (b) to guide the actions of individuals, groups, communities, institutions and corporations, public and private;
- (g) to safeguard and promote the interests of the present and future generations;

Article 16: The impact of life sciences on future generations, including their genetic constitution, should be given due regard.

Article 20: Appropriate assessment and adequate management of risk related to medicine, life sciences and associated technologies should be promoted.

In addition, there is the Council of Europe's Convention on Human Rights and Biomedicine (Oviedo Convention, 1997).^k Article 13 of this Convention states that an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if there is no intention to introduce any modification in the genome of any descendants (see section 3.4.4).

However, current Dutch legislation and legal precedents in the field of healthcare are influenced primarily by the ECHR. The right to self-determination, as specifically protected by Article 8 of this Convention, includes, for example, the right of an individual to make frozen surplus embryos available for research purposes.¹¹⁵ This article also covers the freedom to decide to have children or not and whether or not to make use of artificial reproductive techniques.¹¹⁶

The European Court of Human Rights has not yet made any judgments on the status of the embryo, and there is no agreement on this between the States Parties. When there are differences of opinion on this type of morally sensitive issue, the Court gives States Parties considerable latitude to make their own arrangements, albeit within certain limits.

3.3 EU Regulation: no impediment to permitting use for research purposes

The European Union (EU) has also drawn up regulations and directives relating to gene-editing technologies, in particular three regulations: Regulation 536/2014 on clinical trials on medicinal products for human use, Regulation 726/2004 on the authorisation and supervision of medicinal products, and Regulation 1394/2007 on advanced therapy medicinal products. Also relevant is Directive 2001/83/EC on a Community code relating to medicinal products for human use.

Regulations have direct legal force in the Member States of the EU. EU directives have to be implemented by the Member States, usually by transposition into national legislation. Member States have a certain degree of discretion on how to do this and how they intend to achieve the objectives stated in the directive. Under Directive 2001/83/EC, CRISPR-Cas qualifies as a medicinal product because it meets the functional definition of a medicinal product in Article 1 of the Directive. It is a substance (RNA molecules and a Cas9 protein) that is used to restore, correct or modify physiological functions by bringing about a pharmacological, immunological or metabolic effect (Article 1.2, Directive 2001/83/EC).

Article 90 of Regulation 536/2014 states that no gene therapy clinical trials may be carried out which result in modifications to the subject's germline genetic identity. This prohibition was included in the precursor to the Regulation: Directive 2001/20/EC. In the Netherlands,

^k The full title is Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

the introduction of Directive 2001/20/EC led to amendments being made to the Embryo Act during its passage through parliament. The original text provided for the possibility of eventually lifting the ban on germline modification, but this provision was scrapped from the text of the bill (see section 3.4.6). However, fundamental research into germline modification on embryos in vitro falls outside the scope of Article 90 of Regulation 536/2014 because in this type of research the modified embryo is not transferred to a uterus. This last point is important because according to current legal doctrine an embryo in vitro does not qualify as a test subject.

If the modified embryo is transferred to the uterus for research purposes, Article 90 of Regulation (EU) 536/2014 probably is applicable, because the fetus in that stage of development, during pregnancy, cannot be considered to be an independent entity (person) separate from the woman's body and does not have a legal personality (see section 3.4.1). As a consequence the pharmacological effect takes place in the body of the woman. This means that the procedure is a study of a medicine (gene therapy) that leads to germline genetic modification in the test subject, and that is prohibited by Regulation 536/2014. However, based on the definition of gene therapy in Regulation 1394/2007, CRISPR-Cas is an advanced therapy medicinal product. For this special category of medicinal products, Directive 2001/83/EC (Article 3.7) contains a derogation from the requirement that only registered medicinal products may be placed on the market. Under certain conditions, hospitals may prepare advanced therapy medicinal products for 'an individual patient' without the need for a distribution authorisation. Authorisation for these products is granted by the relevant national authority.

3.4 Dutch legislation concerning the embryo

3.4.1 Legal status of the embryo: no legal person, but a right to protection

Article 1:2 of the Dutch Civil Code considers every individual to be a legal person at birth. This means that a child does not have any rights before birth. However, it is possible to regard a fetus as having been born already as often as its interests require. These interests may relate to things like property law (inheritance) and in legal practice also to non-property law interests, such as child protection measures.¹¹⁷

As long as the fetus is in the uterus, the Dutch justice system provides 'progressive legal protection'. This means that the degree of legal protection increases as the fetus grows, which in turn means that the legal position of the human fetus changes during its development: the protected status of the fetus becomes stronger during the course of the pregnancy as the fetus becomes increasingly viable (capable of living outside the uterus).^{118,119,120,121} An embryo (in vitro) enjoys less protection than an implanted human fetus, which in turn enjoys less protection than an independently viable fetus.

In the literature, some authors argue that the protected status of the unborn child begins from the moment of conception and that when artificial reproductive techniques are used

this legal protection exists from the moment the embryo is implanted in the uterus, because this is then technically the start of a pregnancy.¹²² The moral status of the embryo is discussed further in Chapter 4.

3.4.2 Strict conditions for scientific research involving embryos

The influence of the human rights conventions (particularly the Convention on Human Rights and Biomedicine, see section 3.4.4) on Dutch legislation on legal protection of the embryo can be seen in the Dutch 'Act containing rules relating to the use of gametes and embryos' (the Embryo Act). This law applies to germline genetic modification. It lays down conditions on research involving human sperm and eggs, embryos and fetuses.

In Article 1 of the Embryo Act, an embryo is defined as 'a cell or a complex of cells with the capacity to develop into a human being'.¹ A fetus is defined as 'an embryo in the human body' (Article 1.d). The Embryo Act sets limits on the use of embryos for medical or research purposes in the interests of protecting human dignity and respect for human life, but also recognises the importance of scientific research with a view to improving fertility techniques.¹²³ Balancing these two interests, the law prohibits a number of medical uses of gametes and embryos and permits other uses under certain conditions.

If germline modification is to be considered an acceptable option in principle, scientific research will first be needed on the mechanisms, effectiveness and possible adverse effects of the techniques used. To do this research it will be necessary to culture embryos (see Chapter 2), but this is prohibited under Article 24 of the Embryo Act. However, surplus embryos may be used for research purposes. In view of the embryo's right to protection, such research is subject to a number of strict conditions (Article 10 et seq of the Embryo Act).

Article 3 of the Embryo Act requires that research involving embryos must be approved in advance by the Central Committee on Research Involving Human Subjects (CCMO). No such research may be carried out without the prior approval of the CCMO. The research must meet a number of strict conditions, which apply to research on embryos that will not be implanted in the uterus (preclinical embryo research) as well as to embryos that are implanted (clinical embryo research)..

The rules governing this research are:

1. It must be reasonable to assume that the research will lead to new insights in the field of medical science (Article 10 Embryo Act).
2. The answers to the research questions must not be obtainable from any other methods or type of research (Article 10 Embryo Act).
3. The research protocol must be approved by the CCMO.

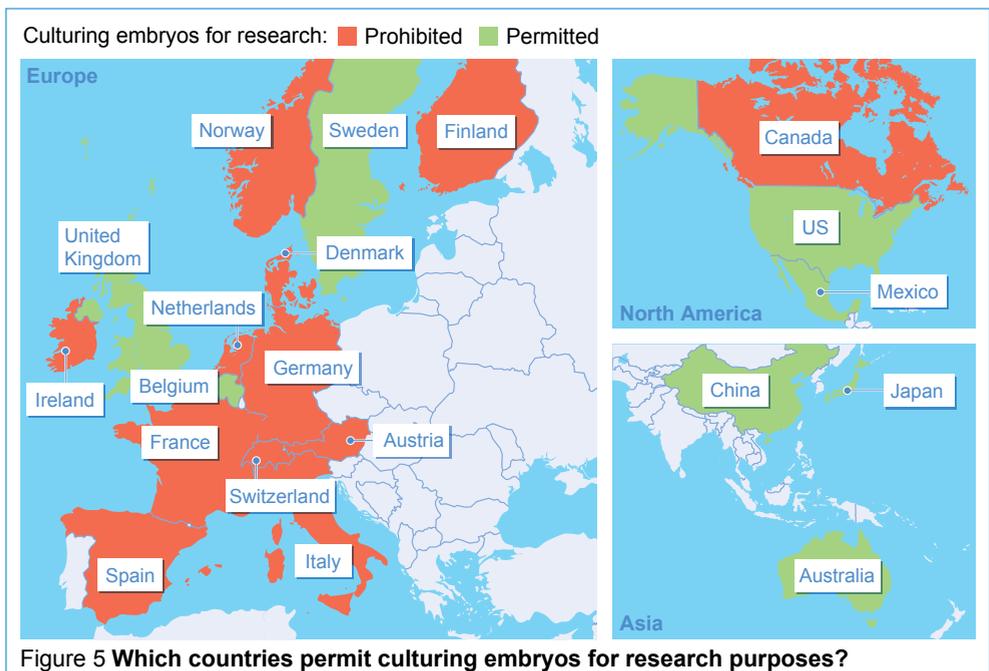
¹ Strictly speaking, this could be interpreted to mean that non-viable embryos such as those used in the study by Liang *et al.* (2015) do not fall under the Embryo Act.

4. The donor couple must have given their consent after having been informed in writing about the purpose and nature of the research (informed consent). This information must be supplied in such a way that it is reasonably certain that the donor couple have understood it. Moreover, the donor couple must be given sufficient time for reflection to enable them to make a carefully considered decision on the basis of the information provided (Article 8 Embryo Act).
5. The embryo must not be allowed to develop outside the human body for longer than fourteen days (Article 24.e Embryo Act).

The fourteen day limit on the duration of the research in point 5 above applies in most countries of the world. One of the arguments for this limit in the Dutch health law literature is that *in vivo* embryos take about two weeks to become fully implanted in the uterus. In the 'law of increasing right to protection' the implantation of the embryo is an important dividing line, beyond which the embryo is given a higher level of protection.^{132,124,135,125,126}

3.4.3 Scientific research involving cultured embryos is prohibited

Some countries permit research on embryos specially created for this purpose (e.g. UK, Sweden, Japan) and other countries prohibit this (e.g. Germany, France, Italy and Spain) (see Figure 5).¹²⁷



The prohibition on culturing embryos for scientific research purposes in the Netherlands is intended to be a temporary measure. Article 33.2 of the Embryo Act states that the prohibition will lapse on a date to be determined by Royal Decree. Articles 9, 11 and 24.b set out the conditions under which embryos may be created for research purposes when the prohibition lapses. These conditions are:

- the scientific research must lead to new insights in the fields of infertility, artificial reproduction techniques, hereditary or congenital disorders or transplantation medicine;
- the research cannot be performed by making use of surplus embryos;
- the written consent of the donor couple must meet the requirements for informed consent which are also required for scientific research on surplus embryos (see articles 5, 6 and 7 of the Embryo Act).

The legislative history indicates that the legislature has made no principle objection to culturing embryos for research purposes, but found that culturing embryos for research is a greater violation of the respect for life than the use of surplus embryos. These embryos are surplus to requirements after an assisted reproduction treatment and would otherwise be destroyed,¹²³ whereas cultured embryos are created solely for research purposes and never to grow and develop into a person (see also Chapter 4). This greater violation of the integrity of the embryo can be justified, according to the legislature, by the importance of research that can contribute to better medical care.

The explanatory memorandum to the Act sets out three reasons why the government decided to introduce a temporary prohibition:

1. the lack of sufficient public support;
2. a desire not to be too out of line with the legislation in other European countries (at that time creating embryos for research was only permitted in the United Kingdom);
3. considering the state of scientific knowledge at that time, the prohibition would not impose a significant constraint on research.¹⁴⁰

3.4.4 No ratification of the Oviedo Convention, but proposed relaxation of the Embryo Act

The Convention on Human Rights and Biomedicine (Oviedo Convention) was drawn up by the Council of Europe in 1997. The Convention was signed in the same year by the Netherlands, with the intention of ratifying it at a later date. However, in 2016, the Netherlands decided not to ratify the Convention, one of the reasons being that it contains a prohibition on culturing embryos for scientific research. According to the Dutch government, this prohibition is no longer consistent with the advances that have been made in reproductive medicine.

Prior to the decision not to ratify the Oviedo Convention, the Dutch health minister commissioned a study to determine whether or not the prohibition on creating embryos specially for research would inhibit clinically relevant scientific and medical developments. The report on this study ('Research into special culture')¹²⁸ concluded, like the two evalua-

tion reports on the Embryo Act,^{55,54} that the prohibition was holding up both fundamental research into early embryonic development and preclinical research into the safety of new reproductive techniques.

Having taken this into consideration, the minister proposed a revision of Article 24 of the Embryo Act to make it possible in the Netherlands to create human embryos for certain research purposes, subject to a number of conditions. These conditions are:

1. the research must be designed to generate new insights and must be directly relevant to clinical practice;
2. the research cannot be performed by making use of surplus embryos;
3. the research design and research activities must meet the relevant quality standards for scientific research;
4. the medical objective must outweigh the objections to creating embryos specifically for scientific research, including any effects on the donors.

The draft bill is expected to be published in mid-2017.

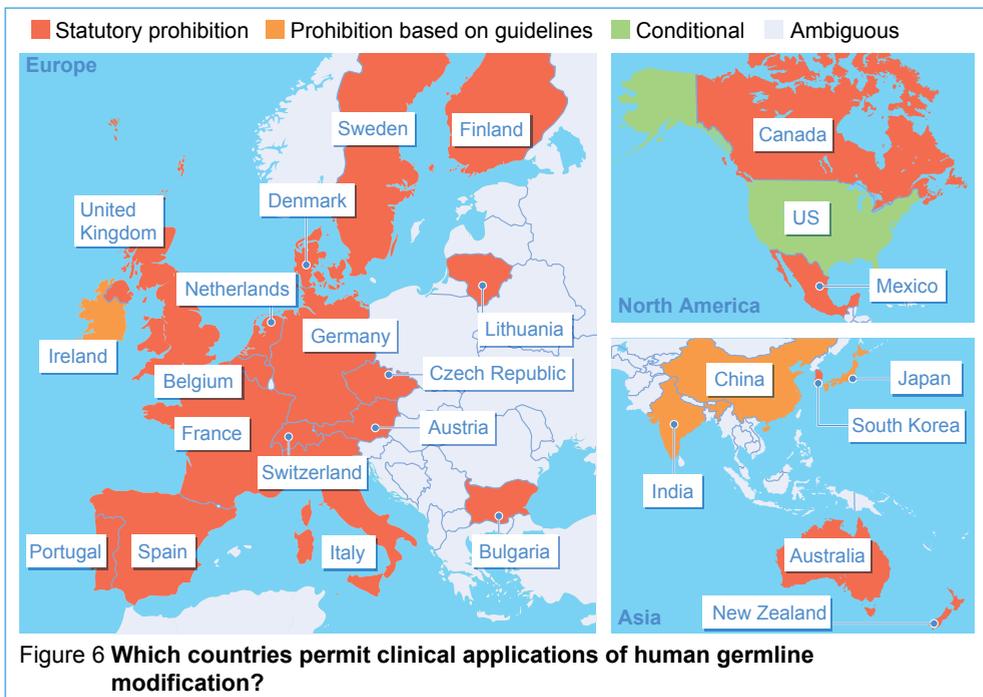
The decision by the Netherlands not to ratify the Oviedo Convention has been heavily criticised in the legal literature. The Convention contains the main principles for biomedicine and patient rights, such as human dignity, equitable access to healthcare, information and consent, the right to a private life, non-discrimination, etc. These authors assert that by not ratifying the Convention the Netherlands puts itself outside the international legal order in the field of medical ethics. It is claimed that in doing so, the Netherlands ignores the importance of European harmonisation and creating a minimum level of protection and human rights in healthcare.^{129,130,131}

3.4.5 Right to decide by those for whom the embryo was created

The Embryo Act contains rules governing who has control over gametes and embryos. These rules apply when gametes and/or embryos are made available for purposes other than 'their own' pregnancy, i.e. for donation or research purposes (Article 8 of the Embryo Act). Control over gametes lies with the adults who made them available (Article 5 et seq of the Embryo Act).^{132,135} The right to decide on in vitro embryos rests with the adults who provided the sperm and eggs, as long as they are also the prospective parents.^{133,135} Control therefore rests with those for whom the embryos were created (the prospective parents).¹³⁴ They must make a joint decision about the future of the embryos. According to the European Court of Human Rights, a prohibition on donating surplus embryos for scientific research is a violation of respect for private life (Article 8 of the ECHR). The Court says that the right of couples to decide what happens to their embryos is an important principle.¹³⁵

3.4.6 Limited germline prohibition: cell nuclear transfers permitted

A second reason why the Netherlands decided not to ratify the Oviedo Convention (besides the prohibition on culturing embryos for scientific research) is that it includes an absolute prohibition on germline genetic modification. The prohibition on germline modification in the Netherlands is limited (see Figure 6).¹⁸⁶ Under the Embryo Act it is prohibited to intentionally modify the DNA in the nucleus of human germline cells with which a pregnancy is to be induced (Article 24.g). From the text of the Act it can be concluded that scientific research involving germline modification is permitted, as long as no pregnancy is induced. The Act also allows changes to be made in mitochondrial DNA, genetic material outside the cell nucleus. According to the legislature, this procedure leaves the key part of the embryo intact: the nucleus containing the genetic traits that influence the development of personal characteristics. Following this line of reasoning, altering mitochondrial DNA is not an unacceptable violation of respect for human life (section 4.3.3).¹³⁶



3.5 Conclusions to Chapter 3

In the Netherlands it is currently permitted, under certain conditions, to carry out research involving surplus human embryos. Culturing embryos for scientific research purposes is prohibited for the time being. This makes it impossible to carry out fundamental research into the early stages of the development of the embryo as well as preclinical research into the

safety of new reproductive techniques, such as cell nuclear transfer and germline modification to prevent genetic diseases in descendants.

The legislature considers creating embryos for research purposes to be a greater violation of the respect for life, and therefore of human dignity, than the use of surplus embryos. The prohibition on culturing embryos for research purposes is a temporary measure. It was introduced because at the time the law was drawn up there was no public support for such research, the Netherlands did not want to step out of line with the legislation in other European countries, and the prohibition was not expected to frustrate scientific progress in the field of reproductive medicine.

Since then the legislation on research involving embryos in several neighbouring countries has been relaxed. Furthermore, with the development of gene-editing technologies such as CRISPR, the prohibition has started to restrict the opportunities for scientific research.¹²⁸ For these reasons, the government has announced its intention to relax the provisions in the Embryo Act. This should make it possible, under strict conditions, to produce embryos for scientific research purposes in the Netherlands.

The use of cell nuclear transfer in clinical practice is legally permissible in the Netherlands, but germline modification is not. The argument put forward by the legislature for this difference is that cell nuclear transfer involves only modification of mitochondrial DNA, which makes up just a small fraction of the cell's DNA and is located outside the cell nucleus.

EU Regulation 536/2014 contains a prohibition on clinical medicine research that involves modifying germline cells of test subjects. The genetically modified embryo in vitro is not considered to be a test subject, which means that this EU Regulation does not stand in the way of a potential future revision of the Embryo Act rescinding the prohibition on research involving germline modification for medical purposes.

4. Ethical discussion

To do scientific research into germline genetic modification and its possible clinical applications, it is necessary to create embryos specifically for this purpose. Quite apart from the legal difficulties, this raises a number of ethical questions. The ethical aspects of research into potential clinical applications of germline modification are the subject of this chapter.

The various opinions and interests that form the context for the discussion of these issues are set out in section 4.1, followed by the arguments about the acceptability of research on embryos and the distinction between surplus embryos and cultured embryos (section 4.2). This leads to a consideration of the desirability of clinical applications of germline modification, addressing the following issues: the value of research into germline modification of embryos, the desire to have one's own genetic children, the interests of the future individual, just allocation of and equality of access to resources, and the arguments surrounding human genetic engineering (section 4.3).

4.1 Context

4.1.1 Diversity of stakeholders

The debate about germline modification touches on the interests of a variety of different stakeholders and involved parties: the public ('non-patients'), patients and parents or prospective parents with a genetic disorder, healthcare institutions, doctors, scientists, NGOs (such as patients' associations for genetic disorders), industry and the government.

These groups each have their own moral or other opinions about the scientific advances being made in the field of germline modification. Moreover, these values and norms can sometimes change over time. There can even be big differences in opinion between people from the same group. For example, some people think that germline modification is a desirable new option, under certain conditions, for preventing genetic disorders being transmitted to subsequent generations; others fear for the acceptance of and care for people with a genetic disorder if germline modification is possible. Some people with a genetic disorder are satisfied with their quality of life or do not feel like a patient (until the disease presents); others are prepared (as yet) to take unknown risks to prevent the disorder being passed on to their descendants.^{32,33}

Some people consider genetic intervention to prevent certain disorders to be a form of discrimination against people with a genetic disorder. They believe it suggests that it is worth trying to eliminate or prevent genetic disorders, which (according to them) in turn implies that people with such disorders are themselves undesirable. Responses to this objection point out that thinking a disease is unwanted does not imply a lack of respect for the people who are affected by it. What are undesirable are the consequences of the

health problems for a child and its family. There is also concern that the care available to people with genetic diseases and handicaps could be reduced if the idea that they are 'responsible' for their disease (because it could have been prevented) becomes generally accepted.

These arguments are not new; they were also made about techniques such as prenatal screening and pre-implantation genetic diagnosis^{137,138,139,m} and these interventions now seem to be widely accepted. This does not mean that society is in complete 'agreement' about these topics, but that there is sufficient public support for making these treatments available, under certain conditions, to people who could benefit from them; in other words, making reproductive options available to couples who are interested in them.

4.1.2 Diversity of opinions

The emergence of the CRISPR technology was accompanied by various articles in the popular science and general press, as well as radio and television appearances by scientists. Some emphasised the potential of the technique for preventing diseases; others painted doom scenarios of a 'super race' and 'designer babies'.

Not long after, in early 2016, the results of the first public opinion polls on the topic were published. A Dutch poll suggested that an overwhelming majority (85% of respondents) would have their DNA altered to prevent the onset of a genetic disease. The respondents were a bit more hesitant about altering the DNA of their children: 65% would have the DNA of their unborn child altered to prevent it inheriting a genetic disease. They were considerably less enthusiastic about altering DNA to obtain resistance to disease (30%) or increase intelligence (15%).¹⁴⁰

This picture is backed up by two American surveys, which also indicated that people are very reluctant to accept genetic modifications in the area of human enhancement.^{141,142} However, these and other studies also indicate that in the US the public are highly critical of germline modification to prevent even serious diseases.¹⁴³

A worldwide opinion poll of 12,000 people from 185 countries shows that many people are critical of germline modification for 'non-health purposes'. Another striking result from this survey is that having a genetic disease or not could not be associated with a positive or negative attitude towards germline modification. This illustrates the diversity of individual opinions within stakeholder and concerned groups, such as patients.

m Because this discussion is not new and is not essentially any different from the discussion about the position of people with a genetic disease and handicapped people in relation to prenatal screening and pre-implantation diagnosis, in this advice we refer to the advisory reports by the Health Council of the Netherlands on prenatal screening (2001, 2016) and on PGD (2006).

Research shows that acceptance of new medical technologies can change over the years.¹⁴⁴ This has happened in the past for things like the contraceptive pill, plastic surgery and in vitro fertilisation.¹⁴⁵ At the same time, there will always be groups of people who have lasting objections to these technologies.

In short, public opinion is not uniform and people's opinions change. This does not mean that the opinions of those involved and of the public at large are not important. Maintaining a record of all these differing opinions can be a useful tool for identifying aspects of importance for governance and policymaking. Opinion polls often use extreme examples (in this case, in relation to diseases and human enhancement) and therefore have little relevance to grey areas and borderline cases, which can only be grasped through a more detailed dialogue. This will be explored further in Chapter 5.

4.2 Research involving human embryos

Further research will be needed before germline modification can be used in clinical applications (see Chapter 2). This research is needed to investigate, among other topics, the safety and effectiveness in practice of genome editing techniques such as CRISPR, and it has to be done on human embryos at a very early stage of development. Scientific research on embryos involves intervening in the early stages of human life. That raises ethical questions about the intrinsic value of the embryo, and not everyone attaches the same importance to this.

4.2.1 Moral status of the embryo

Opinions about the embryo's right to protection vary considerably. This section takes a brief look at the various ideas on the right of in vitro embryos to protection. These ideas can be roughly divided into three groups:^{137, 146, 147, 153}

1. Some people think that as soon as an embryo is created in vitro it has, or should have, the same right to protection as the newborn child. This view can be based on a number of different principles. One of these is that the embryo is a human being, a unity of body and soul. This is a common theme in Christian ethics. There are also theological views that posit a gradual increase in intrinsic value, such as those described in point 3, and theological ideas that attribute intrinsic value to the embryo the moment it is endowed with a soul.^{148, 149} That happens at different times during the development of the embryo, depending on which religious tradition you consult. Another view is that the embryo is a 'potential person' in the modern sense of a person, in which self-awareness is an important criterion. The decisive factor in determining the embryo's right to protection in this view is that it can grow into a human being and that this potential is considered to be worthy of the full right to protection. Whatever the exact details of the principles underlying this right to protection are, people who take this view will never tolerate the use of embryos for research purposes.¹²⁵

2. Others believe that the embryo in vitro has no moral status that can lend it a right to protection. In this view, the potential to grow into a human being is just a possibility and the probability of this occurring depends on whether or not the embryo is transferred to and implants in the uterus. This position does not imply that in vitro embryos can be used for any purpose; the right of an embryo to protection may be based, for example, on its significance to others. This 'symbolic value' may lead to the rejection of a certain use not for the sake of the embryo itself, but out of consideration for the community for which it has a social or moral value.^{125,150}
3. Finally, there is the view that the in vitro embryo has a gradual or developing value. Based on its human origin and its potential to grow into a 'fully fledged' person, the embryo has an intrinsic value that gives it the right to protection. Often this right to protection is considered to increase as the embryo develops.^{151,152,153,154} However, the embryo's right to protection is never absolute. There may be other interests of greater moral value than the embryo's right to protection – but which 'greater moral interests' outweigh the embryo's right to protection?

This last view, of an increasing right to protection, lies at the heart of the current Dutch legislation on embryos and fetuses. In its previous advisory reports, the Health Council of the Netherlands has also declared its preference for this vision.

4.2.2 Research involving surplus human embryos

The current situation in the Netherlands is that research is permitted on surplus embryos, but under strict conditions. In those cases, therefore, it is accepted that the interests of scientific research outweigh the embryo's right to protection.

All research involving embryos is subject to an internationally agreed fourteen day limit on the stage of development beyond which research is no longer permitted.¹⁶⁸ There are various legal and ethical arguments for this fourteen day limit. As discussed in Chapter 3, the legal argument for this limit is that in vivo embryos take about two weeks to become fully implanted in the uterus. Ethical arguments often draw on the 'ontological individuality' proposition: from the fourteenth day an embryo can no longer divide into two and give rise to twins, and so it can be said to have become an individual. There are differences of opinion on the weight that can be attached to this argument.

Other people consider a limit of four to six weeks to be acceptable, because that is the time the embryo is first capable of experiencing sensations and the neural groove and neural tube are formed – the initial stages of spinal cord and brain development.¹³⁷ This view draws an analogy between the beginning of neural activity at one end of the spectrum and brain death at the other: in the same way that a person ceases to exist when the functions of the cerebellum that make consciousness possible are irreversibly lost, a person can only come into being when brain activity first begins and the essential conditions for mental capacities and consciousness are in place.

4.2.3 Distinction between surplus embryos and cultured embryos

As discussed in section 2.6.3, not all categories of embryos are equally suitable for every type of research. Research into germline modification on surplus embryos has its limitations. First, the very earliest stages of development of the human embryo cannot be studied if surplus embryos are used. Second, surplus embryos are already multicellular, which means there is a greater probability of variations (mosaicism) in the intended alterations to the genome than in germline modification of unicellular embryos. This makes it necessary to create embryos for research into germline modification. However, the legislature considers creating embryos for research purposes to be a greater violation of respect for life than using surplus embryos for research (see Chapter 3).¹³⁹

The difference in approach between using surplus embryos and cultured embryos and the different moral values ascribed to them may be derived from the instrumentalisation argument. This argument states that surplus embryos were created originally for use in an assisted reproduction treatment and thus when they were first created they had the potential to develop into a person. They are therefore created not just as a means to an end, but also as ends in themselves. The surplus embryos that are not used in these assisted reproduction treatments are destroyed, unless they are used for scientific research purposes. They can also be used as donor embryos.¹³⁹

If embryos are specifically created for research purposes, we can be certain that they will not develop into persons. They are created solely for the purposes of scientific research. Some people claim that these embryos represent a new category of human life: human life that from the very beginning is destined to have a purely instrumental value rather than an intrinsic and relational value.¹⁵⁵

However, others claim the difference between surplus embryos and cultured embryos is not as clear-cut as this would seem to suggest. They argue that creating more embryos than necessary for an assisted reproduction treatment confers a similar instrumental value on all those embryos. To increase the chances of an assisted reproduction treatment being a success, the usual practice (and always in PGD) is, where possible, to create more embryos than will be implanted in the uterus and more than needed to initiate a pregnancy. It cannot therefore be claimed that all these embryos were created as ends in themselves, because some of them were clearly created as a means to that end, in support of the assisted reproduction treatment itself. It is not possible to say in advance which of the embryos will have the chance of growing and developing into a human person, but it is virtually certain that some of them will never have that chance. This also explains the continuing discussion about whether the creation of embryos for scientific research is qualitatively and morally different – and in particular more instrumentalising of human embryos – from the creation of surplus embryos for fertility or assisted reproduction treatments. In both situations embryos are created as a means to achieve a higher purpose – a pregnancy or scientific research – although some claim that a pregnancy is not simply a means to an end.

For the Health Council of the Netherlands, the instrumentalisation of embryos described above, both for assisted reproduction treatments and for research, is insufficient reason to assume that the cultivation of embryos for research can not be justified. Of course, the perceived need for the research and the ultimate goals of the research are crucial considerations. An aspect that the Health Council of the Netherlands considers to be morally relevant is that egg and sperm donors are needed to create embryos. Moreover, women who donate eggs must bear the risks and discomfort of the donation procedure.^{139,156}

All things considered, the Health Council of the Netherlands is of the opinion that any difference in the degree of instrumentalisation in culturing embryos for important scientific research is not of overriding significance. The Council considers scientific research into germline genetic modification to be of such consequential importance that it justifies the creation of embryos for this purpose. However, the Council notes that it will always be necessary to determine whether or not the research can be carried out on surplus embryos. Only if this is not possible, can the use of cultured embryos be considered as a possibility.

4.3 Clinical applications

The question of whether research into genome editing technologies is acceptable or not cannot be taken separately from the issue of the moral acceptability of clinical applications of germline modification. The answer to this question depends to a considerable degree on what people consider to be a good life. For example, a good life may include learning to live with the disability or constraints that fall to your lot, instead of striving for perfection.¹⁵² However, in Dutch society the desire for a healthy child of one's own is considered normal, as evidenced by the acceptance and funding for reproductive techniques.

Another important consideration is that if germline modification proves to be safe and effective and there are no better alternatives for people with some genetic disorders, doctors may be considered to have a moral duty to make this option available.¹⁵⁶

The Health Council of the Netherlands has previously stated that therapeutic applications of germline modification are in principle acceptable: 'Eliminating a disease in principle justifies modifying the DNA if this brings permanent benefits for the descendants.'^{139,156}

4.3.1 A genetically own child

There are alternatives to germline modification that offer would-be parents with a genetic disorder the possibility of having a healthy child. In the first place, there are alternatives that require a sperm or egg donor, which will make the child only partly genetically their

own. Secondly, there are alternatives which require the prospective parents to abandon any idea of having a genetically related child, such as embryo donation, adoption and foster care.

Couples generally prefer having their own genetic child to adoption or donor insemination.¹⁵⁷ This is shown by the way ICSI (an in vitro fertilisation procedure in which a single sperm is injected directly into an egg) was embraced in the 1990s as an alternative to donor insemination. Although the technique is expensive and invasive (particularly for the woman), there has been little or no debate about the preference for ICSI to donor insemination.¹⁵⁸

There may be psychological reasons why people desire to have children that are genetically their own. One reason is the 'inheritance argument', which, in essence, states that people want to have children so that their genes will outlive them. This has nothing to do with the survival of the human species as a whole, but is all about passing on one's individual characteristics – letting one's genes live on in the history of subsequent generations.

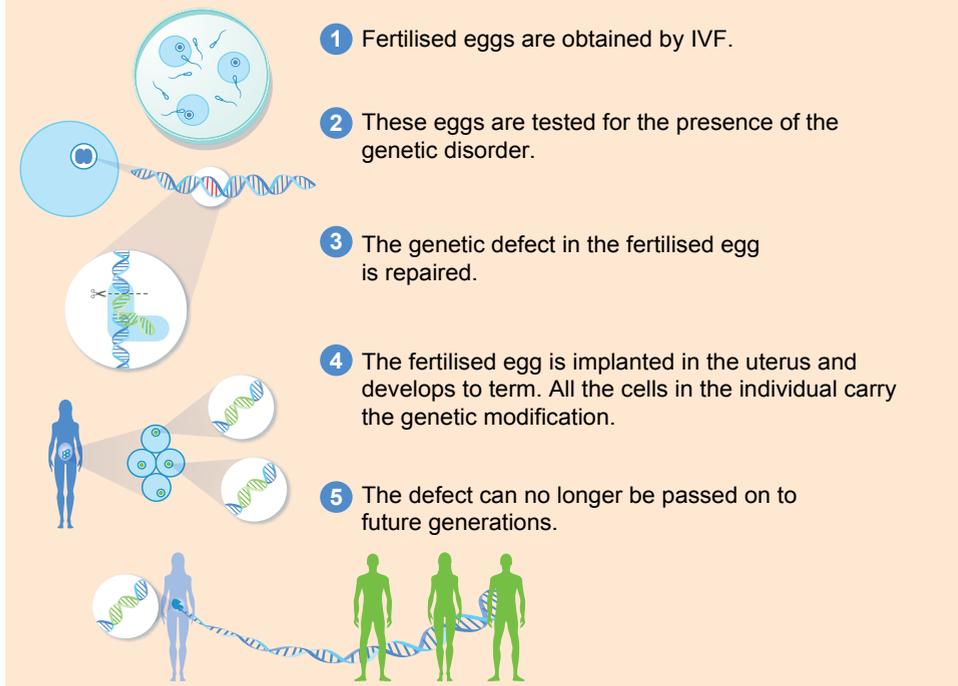
Another factor is the 'recognition argument'. This states that genes influence the characteristics of the individual in a whole range of ways and that genetic kinship leads to recognition. This recognition is important because individuals derive part of their identity from their place in the family history and genetic kinship gives people a sense of belonging. This is more important for some people than others, but it is part of the individual's identity just as much as their social and cultural history.^{159,160}

4.3.2 Alternatives

Prenatal diagnosis and embryo selection via pre-implantation genetic diagnosis (PGD) are alternatives to germline modification that offer prospective parents the option of having a genetic child without (the known) genetic disorders. Prenatal diagnosis involves analysing the DNA in cells of the amniotic fluid or the placenta to determine whether or not the fetus has a genetic disorder. The aim is to give couples reproductive options. A positive (unfavourable) test result gives them the option of choosing to let the pregnancy go to full term and prepare for a child with a genetic disorder, or to terminate the pregnancy.

Embryo selection via pre-implantation genetic diagnosis involves creating several embryos via in vitro fertilisation for prospective parents (of whom at least one has a genetic disorder or both are carriers of the same genetic disorder). The embryos are then tested to see which ones have the disorder and which ones do not. One of the healthy embryos is then implanted in the uterus to initiate a pregnancy, preferably an embryo that does not have the mutation associated with the disorder. However, it is also possible to implant a healthy embryo that is a carrier of the genetic disorder (see Figure 7).

Germline modification



Embryo selection

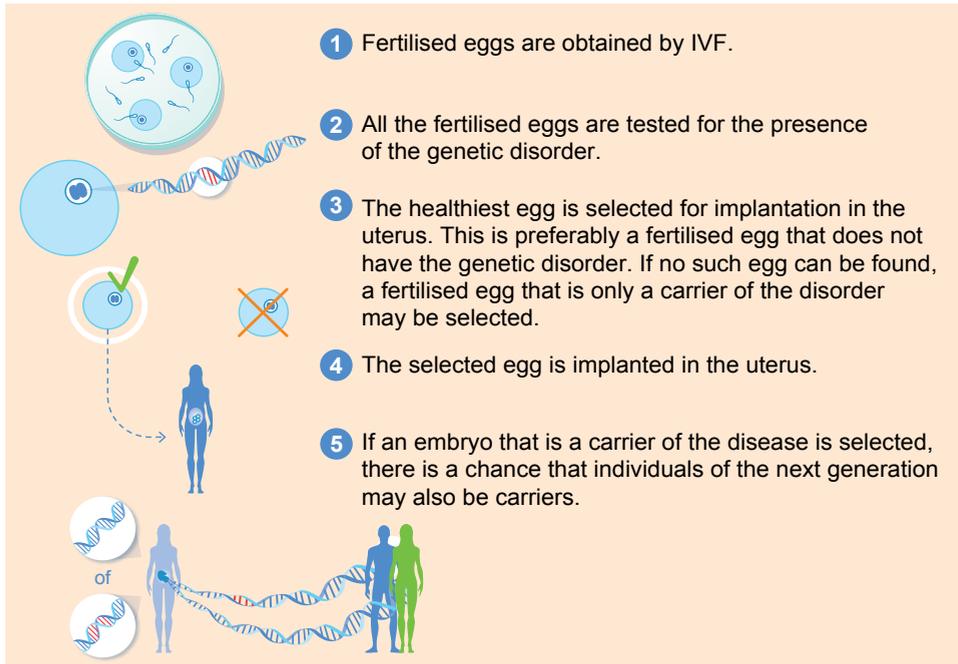


Figure 7 Difference between germline modification and PGD with embryo selection

If after PGD a carrier embryo is selected and successfully implanted in the uterus, the resulting individual will be healthy but will be a carrier of the genetic disorder. If this individual wants to have children and if their partner is also a carrier, any children they have will have an increased chance of inheriting the disorder. This is why it is preferred if possible to implant an embryo that does not carry the genetic disorder.

Embryo selection by PGD in the Netherlands

Pre-implantation diagnosis (PGD) is permitted in the Netherlands. PGD is used most often to prevent the following diseases: Huntington's disease, genetic breast and ovarian cancer, myotonic dystrophy type 1 (Steinert disease), familial adenomatous polyposis coli (FAP), Marfan syndrome, neurofibromatosis type 1, cystic fibrosis, spinal muscular atrophy, fragile X syndrome, haemophilia A/B, Duchenne muscular dystrophy and chromosomal abnormalities for which one of the parents is a carrier.

PGD is not possible in all cases, for example when one of the partners is homozygous dominant for a disorder (e.g. Huntington's disease) or both partners are homozygous-recessive (cystic fibrosis). PGD is also limited by the number of available eggs that can be harvested and fertilised. If PGD is requested for a new indication, this must be submitted to the national PGD indication committee.

There are rare cases in which germline modification is the only option for having a genetic child (see Chapter 2), but even if that is not the case, germline modification can offer advantages over the alternatives described above. When germline modification is efficient, not only the disease itself but also the recessive gene for the disease will no longer be carried by subsequent generations. Moreover, like PGD, germline modification has the advantage of reducing the chances of prospective parents being faced with the distressing choice of whether or not to terminate the pregnancy.

Some scientists expect that eventually fewer embryos will be needed to initiate a pregnancy via germline modification treatments than via PGD. This will depend on the efficiency of the technique used and the quality of the modifications that can be made in the genome of the embryo. However, at the current state of the art of scientific research into germline modification using the CRISPR technology, this cannot yet be confirmed (see Chapter 2).

4.3.3 Human dignity and identity

There are also arguments that can be made against modifying the genome of embryos. Most of these arguments are based on the concept of human dignity, which has a philosophical history and many layers of meaning. Human dignity is considered to be an intrinsic human quality. It is often identified with respect for human life, individual autonomy and the duty to prevent human suffering whenever possible.

Three arguments against germline modification

The first argument against germline modification is the ‘direct’ deontological argument that interfering with the germline contravenes the principle of respect for human dignity and should therefore be considered intrinsically objectionable. For some people in our society, human germline modification will always be unacceptable because it involves artificially changing natural processes.¹⁷²

The second argument is the ‘indirect’ consequentialist argument that with current knowledge any possible negative effects remain unknown, which makes any use of the technique by definition irresponsible.¹⁷² At the moment there is an international consensus on the position that under current knowledge, and given that the seriousness and magnitude of the risks cannot be foreseen, making specific alterations to human germline cells is irresponsible. Not enough is known about the possible negative consequences for individuals conceived from modified germline cells, or about the consequences for future generations. As indicated above, the concerns are about the irreversible nature of the changes once individuals with germline modifications have become mature.

The third argument rests on the recognition of the human right to inherit a genotype that has not been purposely modified. This argument is a defence of human autonomy, because future individuals who have to live with the consequences of changes made to the germline are not given an opportunity to give permission for those changes to be made. This argument can be countered by the fact that no-one can ever be in a position to agree to their genetic make-up. However, when modifications are made to germline cells, the parents of such individuals make decisions (often irreversible) for their future children. Some people argue that this restricts the child’s right to self-determination and fundamentally changes its relationship to its parents (its ‘makers’).^{153,172,166,162}

The argument for germline modification as a form of respect for human dignity

As described in section 3.2.2, the statutory difference between cell nuclear transfer and germline modification is based on the assumption that modifying mitochondria does not fundamentally alter the cell’s DNA. According to the law, cell nuclear transfer leads to a minimal alteration in the genetic identity. The procedure leaves the key part of the embryo intact – the nucleus containing the genetic traits that influence the development of personal characteristics. In contrast, modifications to DNA in the cell nucleus do lead to changes in the genetic identity of the embryo. However, research shows that although mitochondrial DNA makes up just a small amount of the total DNA in the cell, it also has a very important function (see Chapter 2). Moreover, whether a modification of the DNA changes the identity of the embryo or not is not just a scientific question, but a philosophical one as well.

For one thing, any change of identity is crucial in determining whether or not germline modification prejudices the interests of the future child, such as its right to an ‘open future’. The principle of an open future holds that each child has the right to conditions necessary to

develop into an autonomous person. This means that parents have the obligation to ensure that their children have the broadest possible range of life choices.¹⁶³

Since Aristotle, a distinction has been made between qualitative identity and numerical identity. Qualitative identity is when two things or people have the same characteristics or qualities. Identical twins are qualitatively identical; they are not numerically identical because they are two different people. An important but difficult question in the discussion is what changes in the DNA of an individual can be made without these causing a change in numerical (or ontological) identity, which therefore results in the creation of a different person. The literature contains different opinions on whether or not cell nuclear transplants cause a numerical change of identity.^{164,165,166}

If altering the DNA in mitochondria or the cell nucleus does indeed lead to a change in the numerical identity of the embryo, the implications are clearly important. These changes cannot possibly adversely affect the future child, because this specific child was only created after the modification; neither can the interests of that future child be prejudiced, and therefore its right to an open future is not compromised. It should be noted, though, that many people may consider that the embryo is in any case not identical to the person who later develops (see section 4.3.1). The question then is not whether we should be permitted to modify future children or not, but what sort of children we wish to create using this technique.

If numerical identity is not changed, the question then is whether or not a germline modification would prejudice the child's right to an open future. Modifications made to the genome of an embryo that lead to qualitative changes in the future person from someone with to someone without a serious disease would in fact expand rather than restrict the child's range of possible futures. As long as changes in the DNA in the cell nucleus have the effect of preventing a serious disease, there is no reason to come to a different judgement regarding the effect on identity.

Based on this line of reasoning, in 2001 the Health Council of the Netherlands concluded that cell nuclear transplants to prevent mitochondrial disease does not violate human dignity.¹⁵⁶ On the contrary, if the aim is to prevent suffering by removing the cause of a disease, cell nuclear transplants should in fact be considered a form of respect for human dignity. As long as the technique is safe, replacing the unhealthy mitochondrial genes with healthy ones does not prejudice the interests of the future persons, but rather serves them. This reasoning also applies to germline modification – as long as the technique is safe.

4.3.4 Human genetic engineering and designer babies

In theory, gene-editing technologies can do much more than just prevent serious genetic disorders. In future it may be possible, for example, to reduce the risk factors for things like cancer and cardiovascular diseases, or to activate or deactivate genes involved in disease resistance (such as HIV). Mention is also made in the literature of the hypothetical prospects

of modifying people's genetic make-up to give them specific attributes by way of intelligence, outward appearance or physical capacities.⁹⁷ For some people this is unthinkable and unacceptable, while others consider it to be simply an extension of the possibilities already available to parents to 'shape' their children.^{167,168,169,162}

Prospects such as these fuel discussions on whether it should be possible to use new techniques such as germline genetic modification for human enhancement, or that limits should be set on the engineering of human life.

The concept of 'human enhancement' is a difficult one to define.¹⁶⁹ Some interpret 'enhancement' as covering all possible ways of improving ourselves and how we function, a broad definition that includes wearing glasses and the invention of writing.¹⁷⁰ Others make a distinction between enhancements made through technological interventions in human biology and those achieved in other ways.¹⁷¹

What the various definitions have in common is that they all have to do with enhancing human characteristics or functions. These enhancements can be made on three levels:¹⁶⁹

(1) improving abnormal functioning; (2) optimising and perfecting normal human capacities; (3) adding and creating whole new capacities. Often a distinction is made between medical treatments (1) and enhancements (2 and 3), but this distinction is not always clear-cut. Problematic areas include enhancements made to prevent diseases, such as reducing risk factors or strengthening immunity, which could be called 'medical enhancement'.

Enhancement is often associated with the history of eugenics, and for many people this is synonymous with the Nazi regime during the Second World War, which forcibly sterilised and murdered specific groups of people in an attempt to create a 'master race'. However, the history of eugenics is much more wide-ranging. At the start of the twentieth century eugenics legislation was in force in the US and across Europe, some of which remained in place until the 1960s. The big difference between the old forms of eugenics and the current applications of PGD is that in the past people were forced or coerced into undergoing tests in the service of a government vision of what people should be like, whereas current eugenics is based on voluntary participation as an expression of individual reproductive autonomy.¹⁷²

Nevertheless, various critics argue for restraint in developing and using germline modification for purposes of human enhancement or improvement. They warn against the dangers of interfering with nature and the effects this could have on society, interpersonal relations and human dignity. They think it is especially important to realise that the distinction between 'normal' and 'sick' or 'diseased' has shifted throughout the ages. The increasing possibilities for diagnosis and treatment may make people more inclined to seek a medical response, which raises the question of where the dividing line between healthy and sick should properly lie, now and in the future, and by extension where the dividing line should be between proper and improper uses of germline modification for medical purposes.

The 'slippery slope' argument is often used to express the fear that permitting research into a medical application of germline modification will eventually lead to the use of genome editing technologies for non-medical purposes.^{156,173} A key assumption in the slippery slope argument is that once a development has been set in motion (a new technology is investigated or accepted) there is no turning back.¹⁷⁴ There are two types of slippery slope argument: logical and empirical.¹⁷⁵ In a logical slippery slope argument, it is logically impossible to defend a standpoint without also defending subsequent standpoints that logically follow on from the first but which one wants to reject. In the case of germline modification, there is no logical slippery slope. An empirical slippery slope can be halted or diverted by imposing regulations, and there is evidence that this could be the case for germline modification. For example, experiences with regulating PGD give no cause to fear a slippery slope towards human enhancement. Moreover, the experts do not agree on whether or not improving multifactorial characters such as intelligence and sporting performance will ever be possible at all.¹⁰⁸ The theoretical possibility of an empirical slippery slope is insufficient reason for a ban on medical germline modification, but it does underscore the need for continual debate about the desirability and regulation of germline modification (see also Chapter 5).

4.3.5 Equality and justice

Some social scientists and various NGOs are concerned about the desirability of germline genetic modification from a broader social perspective. They fear that germline genetic modification will widen existing differences between people because this technology will be available only to a select group. They predict a widening of the gulf between rich and poor, and by extension the creation of a gulf between the enhanced and the unenhanced. In many countries people have little or no access to assisted reproduction technologies to prevent or reduce the risks of passing on a genetic disorder. On the other hand, it can be argued that unequal access to something is not a reason for denying *everyone* access to it. The solution should not be to take a levelling down approach, but to correct the inequality by giving the less endowed access to it as well.

Besides the issue of equal access to technology, there is the question of the social value of technology. How do we determine whether or not we can justify investing in germline modification for future generations, but not, or to a lesser degree, in the development of therapies and treatments for existing patients? Social value is a generic issue in medicine and is also applicable to embryo selection. Even if there are no moral objections to germline modification, the question of whether or not society will be prepared to pay for such treatments must be answered.

Finally, the acceptability or not of 'moral free-riding' on scientific research which is banned in the Netherlands has to be addressed. If the research is considered to be morally unacceptable in the Netherlands, the Health Council of the Netherlands argues that the results of such research carried out elsewhere should not be used in the Netherlands either.

4.4 Conclusions to Chapter 4

Numerous stakeholders are involved in the debate about the desirability and acceptability of germline modification. At the moment little is known about the possible clinical applications and risks. It is therefore not possible to come to a clear and definite conclusion about the acceptability of germline modification, but it is possible to investigate the conditions under which clinical applications of germline modification could be practised. Important among these is early consideration of the position of patients and access to the technology.

If germline modification is considered to be a morally acceptable option for preventing genetic disorders from being passed on to future generations, research involving cultured embryos will be needed. This raises questions about the embryo's right to protection and the distinction between surplus embryos and cultured embryos. Dutch legislation is based on an increasing intrinsic value, leading to an increasing right to protection for the embryo. The Health Council of the Netherlands has also taken this position in various advisory reports. It means that the embryo deserves protection, but that there may be more important interests that outweigh this right.

The Health Council of the Netherlands is of the opinion that if there is a moral difference between embryos created for assisted reproduction treatments (but which were not used for this) and embryos specifically created for scientific research purposes, this difference is not so important that it justifies a prohibition on culturing embryos for research purposes. When scientific research can only be done using cultured embryos, creating embryos for this purpose can be justified. A morally relevant difference between surplus embryos and cultured embryos is the discomfort or inconvenience that may be caused to egg and sperm donors. The Health Council of the Netherlands is of the opinion that scientific research can be important enough to justify asking a woman to donate some of her eggs, even if this does not increase her own chances of a successful IVF treatment, but that she must be fully informed of the purpose of the research using her eggs and agree to this beforehand.

Scientific research with cultured and surplus embryos must meet the same criteria, with one additional criterion based on the subsidiarity principle: surplus embryos should be used for research purposes whenever possible; only when this is not possible can it be justified to create embryos specifically for research into germline modification.

Regarding the clinical application of genetic modification, the Embryo Act makes a distinction between germline modification and cell nuclear transfer. The Health Council of the Netherlands thinks this is inconsistent. If the argument is that the changes in mitochondrial DNA that accompany cell nuclear transfer do not lead to a change in identity, there is no reason to believe that the same should not also be true for certain changes in the cell nuclear DNA made during germline modification. Both interventions can lead to qualitative changes in the future person, from someone with to someone without a serious disorder.

COGEM and the Health Council of the Netherlands observe that it is not always easy to make a distinction between the treatment of genetic disorders and human enhancement (e.g. improving intelligence). This complicates the discussion about the boundary between acceptable germline modification used as a curative and germline modification for disease prevention or human enhancement. Good decision-making depends crucially on first conducting a dialogue about the conditions under which the use of germline modification can be acceptable, with due consideration to the added value of this technique relative to existing alternatives.

5. Points for consideration by government, science and society

As we have seen in the previous chapters, human germline modification raises a number of ethical and legal questions. It is unlikely that consensus will be reached on this subject any time soon, which is particularly unfortunate given that advances in the field of germline genetic modification are now moving at such a fast pace.

COGEM and the Health Council of the Netherlands are of the opinion that technology does not develop entirely autonomously, but is steered to a significant degree by human decisions. Ultimately it is people in various positions in society – politics, government, patients' groups, fundamental science, medicine – who decide on research funding, determine the legal limits of this research and how it is assessed and regulated, prioritise research topics, and carry out preclinical studies and clinical trials. Of course, decision-making can also be influenced by uncontrollable or unpredictable social processes.

In short, steering the development of technologies requires the active participation of government, science and society, which makes it important that stakeholders and interested parties determine their positions on germline modification. This does not necessarily mean that a consensus has to be reached, but it does mean that government, science and society must agree on who decides what and when, and on the basis of which arguments. This is called governance.¹⁷⁶ There are various models and levels of governance, such as governance oriented towards public participation or sustainable innovation and governance organised at the local, national or international level.¹⁷⁷

Given the nature of this technology and how it has developed, an international form of governance would seem to be most appropriate, but national governments will also have to think about what position they should take within their own national borders; if they do not, the international context will decide for them.¹⁷⁸

This chapter explores the main governance issues surrounding germline modification in the Netherlands for government (section 5.1), scientists and medical professionals (section 5.2), and society (section 5.3). In the short term, the key issues will concern research on embryos, both in the national and international contexts.

5.1 Government

The government plays a key role in weighing up the different arguments about germline modification. It has to make policy that takes account of the scientific possibilities and the range of needs and opinions in society. That policy must do justice to the diverse interests

in society, such as preventing serious suffering and respecting individual freedom of choice. But the government also has a responsibility for science and innovation.

This double responsibility is reflected in the response by the environment, health, science and economic affairs ministers to the *Trend Analysis Biotechnology 2016* report by COGEM and the Health Council of the Netherlands. In their letter the ministers describe the role of government as providing opportunities and setting limits in a way that protects individuals and society while minimising restrictions on innovation.¹⁷⁹

5.1.1 Research: legislative review needed

In the short term, the most important question for the government is whether or not to expand the possibilities for research on human embryos; in other words, whether or not to amend the Embryo Act. This law leaves room for new developments and shifts in public support, which was the legislature's intention when the Act was drafted. To keep the options open for such amendments, the health minister announced that the Netherlands would not ratify the Convention on Human Rights and Biomedicine (section 3.2.7) and that a bill making it possible to create embryos for research purposes would be prepared and put before parliament.¹⁸⁰ Various scientists argue that creating embryos for fundamental research is also essential^{181,182} (section 2.5). The minister expects this will be possible under her proposed amendments to the legislation.¹⁸³

Assessing the safety of new technologies is a government responsibility, but if necessary part of this work can be delegated to licensing authorities, advisory bodies and review committees. In the Netherlands, medical research (involving embryos and gametes) is reviewed by the Central Committee on Research Involving Human Subjects (CCMO) and by the regional Medical Research Ethics Committees (MRECs). Clinics that offer IVF and PGD and store and use human tissue must obtain a licence from the Ministry of Health, Welfare and Sport. Finally, the government can decide to steer the direction of research and innovation, for example through its decisions on research funding.

5.1.2 Application: criteria for embryo selection

Whether or not germline modification becomes available in clinics depends not only on scientific progress, but also on the laws and regulations that facilitate, discourage or prohibit it.¹⁸⁴ If it is decided that germline modification is acceptable in the Netherlands, the Embryo Act will have to be amended to allow cultured embryos to be used for research purposes.

Current EU regulations and directives do not prevent the amendment of Dutch legislation to permit the culturing of embryos for in vitro research. However, the situation will become more complicated as the prospect of clinical trials involving the implantation of modified embryos in the uterus draws near (section 3.3). To make clinical trials with germline modification possible, legislation will be needed setting out the conditions under which this can

be permitted and the criteria against which the research should be reviewed. Possible conditions have already been proposed in international discussions.

In February 2017 the *US National Academy of Sciences* concluded that clinical trials with germline modification should be possible within a robust and effective regulatory framework, subject to strict conditions. The report by the Academy proposes an initial set of conditions for consideration (see text box).

Possible conditions for clinical trials for germline modification

The *US National Academy of Sciences, Engineering and Medicine* has formulated the following conditions for the clinical application of techniques for human germline editing:

- they may only be used in the absence of reasonable alternatives;
- they may only be used to prevent serious diseases or conditions;
- their use must be restricted to editing genes that have been convincingly demonstrated to cause or to strongly predispose to that disease or condition;
- their use must be restricted to converting such genes to versions that fall within the natural variation associated with healthy individuals;
- their use is conditional upon the availability of credible preclinical and/or clinical data on risk and potential health benefits of the procedures;
- during trials there must be rigorous monitoring of the effects of the procedure on the health and safety of the research participants;
- trials must be accompanied by comprehensive long-term, multigenerational monitoring that respects personal autonomy;
- trials must satisfy the requirements of maximum transparency and respect for the privacy of patients or research participants;
- there must be continued reassessment of both health and societal benefits and risks, with broad participation and input by the public;
- trials must be subject to oversight mechanisms to prevent extension to uses other than those permitted under these conditions.

It is up to the government to initiate a process for drawing up detailed regulatory conditions for germline modification, but this should be done in dialogue and cooperation with scientists, medical professionals and society.

The first clinical applications of germline modification could be done in accordance with the criteria for PGD, for which a regulatory framework is already in place. In the Netherlands there is a list of disorders for which PGD is possible and for which parents are permitted to screen out affected embryos (section 4.3.2).

New indications are being investigated for the national PGD indication committee.¹⁸⁵ The criteria used for this could also provide a framework for assessing candidate disorders for germline modification. A case-by-case approach led by a review committee could in time

lead to the creation of a tiered classification of indications for which germline modification is permitted.

The fact that new reproductive techniques for preventing genetic disorders are still becoming available (e.g. PGD, germline modification) may in time have an impact on the health-care system. Even if the number of people with a genetic disorder declines, the government will still have a duty to provide them with medical care, however small the group of patients. The government also has a responsibility for patient choice and for access to technology and medical facilities, and here too there are social justice issues at stake: how can the costs of expensive therapies be justified if, for example, this means that alternative or preventive measures are not provided?¹⁷⁸

And if the Dutch government upholds the prohibition on germline modification, it will still have to prepare for a future with germline modification. If germline modification is permitted in other countries, 'medical tourism' will be inevitable.^{186,187}

Medical tourism for assisted reproduction techniques (ART) is already growing, for example for diagnostic tests (such as NIPT) and gender selection of embryos.¹⁸⁶ Concern has been expressed about the fact that some countries are investing considerable time and effort in the governance of ART, but other countries are less rigorous in their approach and allow clinics to offer services for the selection or modification of embryos before the safety and efficiency of the techniques have been properly assessed.^{188,189}

Medical tourism usually escapes the notice of official bodies and often only comes to light when complications arise. The Dutch government has little influence over this phenomenon and cannot ban medical tourism, but it can help by informing the public.

5.1.3: Opinion-forming: essential in support of decision-making

Clinical applications of germline modification are currently not an option. Nevertheless, the government, the scientific community and society at large will have to start thinking about the implications of this technology now to ensure that ethical and social considerations are not just 'bolted on' when clinical applications do become available.^{46,188}

Although identifying possibilities and risks is largely a task for scientists and risk assessors, the evaluation of the acceptability or not of clinical applications is a job for society and politicians. It is therefore essential that research into the safety and efficiency of germline gene-editing techniques is accompanied by activities to facilitate opinion-forming among stakeholders and interested parties.

When biotechnological developments raise issues affecting social values and norms, the government's view is that it is first up to those directly involved (researchers, doctors, industry) to take appropriate action. This position is reflected in the above-mentioned response by the ministries of environment, health, science and economic affairs to the *Trend Analysis*

Biotechnology 2016.²⁰² The government can contribute its own views, facilitate procedures and (at the end of the process) amend legislation as required. The same goes for the dialogue with civil society: the government believes it should only set the regulatory framework and amend legislation where necessary once the debate has come to a conclusion. However, this position is open for discussion.

According to COGEM and the Health Council of the Netherlands, opinion-forming should not be limited to practitioners and healthcare providers (even initially). It is important to get broader groups in society – as potential patients or parents facing a choice – actively involved at an early stage as well. Reflection, opinion-forming, public participation and consultation are essential in determining whether or not a ‘socially robust’ and legitimate application of germline modification is possible. They form a crucial basis for political decision-making on whether or not to permit the use of germline modification.

It is important to hold an open and critical debate that will generate insights, articulate arguments and form opinions. In this context, opinion-forming must not be seen as an end in itself or as a problem that has to be ‘solved’. Stakeholder participation is an important instrument for gathering different types of knowledge and views in support of the political debate and the policymaking process.

The government has a key role to play in facilitating this dialogue at an early stage, for example by organising meetings of stakeholders and interested parties to identify opportunities and challenges. When government-funded research is accompanied by public participation, the preclinical and clinical stages are more likely to better reflect the wishes and needs prevalent in society. The government is also an important player in providing independent information on the possibilities and limitations of and alternatives to germline modification.

5.2 Scientists and medical professionals

Scientists and medical professionals (doctors and healthcare providers) are directly involved in the development and application of new medical technologies such as germline modification. Researchers provide answers to questions about the impact and safety of gene-editing techniques for various applications. Medical professionals are in contact with researchers and patients and have a responsibility to their patients to ensure that any new medical treatments they receive are both safe and appropriate. The range of views on germline modification illustrate the importance of the medical professions in the acceptance of new techniques by both the government and society.⁷

5.2.1 Research: science confronted by legal and ethical boundaries

The boundaries of medical research are not determined solely by the scientific state of the art, but also by the legal and ethical limits on what is considered to be acceptable research.

Following publication of the first experiment in which DNA in human embryos was altered using CRISPR technology, it was intimated in the media that in Asian countries, such as China, this type of activity is not subject to any form of regulation. This was denied by researchers in other articles.¹⁹⁰

Nevertheless, there are big differences in national legislation on research involving human embryos, even between countries such as the Netherlands and Belgium. These differences could (unintentionally) lead to a 'race to the bottom' in the pursuit of scientific prestige or commercial profit. If this happens, countries where the regulatory framework is patchy or largely non-existent are likely to become 'risk havens', while other countries tighten up their regulatory restrictions. The legal position and protection of researchers may then come under pressure.

Differences in national legislation also present dilemmas for medical journals. Authors of papers published in these journals are required to provide a written declaration that their research was carried out in accordance with legislative and regulatory requirements and that any necessary permissions were obtained from the relevant ethical committee. However, differences in national legislation may lead to situations in which articles are submitted on research that is prohibited in many countries or considered to be unacceptable by the scientific community.¹⁹¹ On the one hand, one can question whether this type of research should be reported at all, because publication carries the risk that it will acquire an international stamp of approval. On the other hand, the case can be made that it is important that these studies are published and are not kept 'under the radar'. Their publication initiates debate and other scientists are able to benefit from the results and learn from the problems identified. At the same time, the morality of other countries with a stricter legal and ethical framework making use of such research results can be questioned (moral free-riding).

Various national and international organisations and professional groups have stressed the importance of research into germline modification of human embryos.^{192,193} However, several questions about the safety and efficiency of germline gene-editing techniques are not purely scientific or technical in nature, or ethically neutral, and it is important that researchers remain alert to the moral character of scientific issues.¹⁹⁴ Such issues require broader stakeholder discussions with medical professionals, patients' associations and other social parties on questions such as what diseases have priority in research on germline modification, what is an adverse effect and what effects are unacceptable. Care should be taken in such discussions to prevent unrealistic expectations among potential beneficiaries, such as patients and prospective parents.

5.2.2 Application: acceptable risks are also a social and political issue

An obvious point for consideration is making the technique safer and reducing the risks. Nevertheless, even after extensive scientific research, uncertainties will remain and the only way these can be removed is through practical application of the technique. Scientific research alone can never demonstrate that something is 100% safe.

A key question is when the risks are small enough and the benefits big enough to justify the practical application of germline modification. The medical professions can provide an answer up to a certain point, but it still remains a social and political question. Answering it requires a form of governance in which social actors are involved in the design of research and practical applications from an early stage.

Medical professions have a duty to provide full and balanced information on the treatment method and possible alternatives, with the best interests of the patient (or future child) in mind and with full transparency about the possible uncertainties and risks.¹⁹⁵ On the basis of the possibilities and available information, prospective parents should be in a position to make a well-considered choice that is consistent with their personal wishes and beliefs. In principle, this is no different than for other reproductive techniques, such as IVF and PGD.

In addition, the possible clinical applications of germline modification should be subject to good governance over the long term. This must cover things like whether and how the first children to be born following an assisted reproduction treatment using germline genetic editing are to be monitored during their lives in order to identify and investigate any unanticipated effects.

5.2.3 Opinion: critical reflection by the medical professions

Soon after the discovery of the CRISPR gene-editing technology various scientists raised the alarm about the major impact it will have on medicine. Not long after, the *US National Academy of Sciences* announced an international summit to discuss the subject,¹⁹⁶ but there were doubts about the validity of this type of discussion. The criticism was that in this type of forum it is mainly scientists who decide on the type of regulation that should be adopted,^{197,198,199} and that they are not independent enough and do not have the requisite democratic legitimacy to take decisions about technologies that could have a major impact on society.²⁰⁰ Similar criticisms were made in 2015 in the United Kingdom in response to legal proceedings on the acceptability of cell nuclear transfer.^{201,202} The critics argued that the final decision on this case was based primarily on technical and scientific arguments and that too little weight was given to the outcome of the public consultation.^{203,204,205} This is an essential consideration in the discussion on germline modification.

From the literature it is apparent that some researchers, medical professionals and ethicists are wary of the premature use of new techniques without first investigating their safety and the public's acceptance of them.^{3,4,5,66} Other scientists and ethicists emphasise the possible benefits and talk of a moral duty to use germline modification.^{5,206,207} They make the case for proceeding rapidly with research into safety and possible applications. This shows that opinions on germline modification and other modern reproductive techniques differ widely, even among scientists and the medical professions.

Divergent views among scientists and medical practitioners

The birth of the first child conceived using the maternal spindle transfer technique was announced in the autumn of 2016 and generated international debate. Directly after that came the report that pronuclear transfer had also been used in Ukraine. These techniques for cell nuclear transfer had been featured extensively in the news when in 2015, after four years of discussion, they were legally permitted in the United Kingdom. But while the first child resulting from these techniques was yet to be born following this long consultation and decision-making process, doctors in other countries were already using these techniques, in some cases by sidestepping the legislation. Critical questions were raised by the medical professions: was this in the best interests of the child, or simply to gain scientific prestige?

This case raises the question of whether self-regulation alone can guarantee safe and responsible clinical applications.

These differences of opinion are also found among patients and parents. Some are prepared to take potentially large and unknown risks for their unborn children, whereas others have no interest in a germline modification option.^{34,208} The medical professions will have to come to an agreement among themselves on which risks are absolutely unacceptable and which can be justified. Given the discussions on the dividing line between disease and health and between healing and enhancement, these groups have a major responsibility. Patients and patients' associations can also make important contributions to this dialogue.

5.3 Society

Although patients and prospective parents with a genetic disorder eventually have to decide for themselves whether or not they want to make use of germline modification, its desirability and acceptability is a wider issue of relevance to the whole of society – and society consists of people with diverging views formed within differing national, cultural and/or religious contexts.

5.3.1 Research: stakeholder involvement in research agenda crucial

Society as a whole is not directly involved in scientific research into germline modification. Making surplus embryos available for scientific research is first and foremost a choice to be made by the prospective parents for whom the embryos were created in the first place. The public appears to have few objections to this state of affairs, but this may not be the case for the creating of embryos purely for research purposes. Besides, some groups and individuals will be categorically opposed to creating and using human embryos for research purposes. Nevertheless, this type of research can also be seen as being in the collective or public interest as the aim is to prevent future suffering.

For these reasons it is crucially important to critically review the need for such research and any ethical issues, taking into account the contribution to the public interest made by the research. Such reviews are already made when surplus embryos are used for research purposes in the current situation. Opinions are divided on whether or not there is a fundamental difference between surplus embryos and cultured embryos (section 4.2.3). To meet the requirements of informed consent, donors of gametes that are used to create these embryos should be fully informed of the situation beforehand.

Patients, patients' associations and prospective parents may have an interest in research involving human embryos. Fundamental research does not usually lead directly to applications or new clinical treatment methods, but it does form the basis for applied research. It is important to make this connection, even though it is not always obvious. A debate between the scientific community and society is vital to ensure that medical innovations in this field are responsible and can count on public support. A first step could be to involve those directly affected, such as patients and prospective parents with a genetic disorder, in drawing up the research agenda.

5.3.2 Application: protecting vulnerable groups and managing medical tourism

The governance of germline editing applications will mainly involve parents and prospective parents with a genetic disorder, patient groups, healthcare institutions, doctors and the government. But once this technology becomes available, attention will shift to the position of members of the public with a genetic disorder. Like embryo selection, germline modification can in time lead to a reduction in the size of some patient groups. On the one hand this is positive, because fewer people will be faced with the prospect of serious suffering, but on the other hand the position of the existing patients may worsen – either for practical reasons (such as fewer possibilities for care and insurance) or due to social effects (such as discrimination and a lack of understanding). In practice, neither the government nor the medical professionals can exert much influence over these types of social processes. Nevertheless, the government does have a responsibility to promote choice and equal treatment, as well as to protect vulnerable groups in society.

Medical tourism is a realistic prospect given the differences in access (costs, criteria) and acceptability of medical treatments around the world.^{186,209} The Dutch government has little direct influence over this phenomenon and cannot ban or control medical tourism. The most it can do is establish an information platform where patients and prospective parents with a genetic disorder can find answers to their questions. Many prospective parents will nevertheless not be inclined to look for information from formal bodies, because treatments are not permitted in the Netherlands anyway.

5.3.3 Opinion-forming: doing justice to diverse opinions and values

Reaching a consensus about a delicate subject such as germline modification is an impossible task in a heterogeneous society and certainly across an international community. The

frequent calls for a wide-ranging public debate to reach a consensus seem logical enough, but say little about how decisions should be taken and by whom. Experience shows that the public debate starts the moment scientific developments are covered by the media. It is therefore not up to the government to start this debate, but to pick up on it and, in discussion with stakeholders and interested parties, to explore the limits of what is acceptable and where there is room for individual responsibility and choice.¹⁷⁶ Such discussions can include the conditions and criteria for making this technique available to people who want to make use of it. However, not everyone will want to take part in such a debate or exercise a choice, because some people will have no need or desire to make use of this technology, just as for IVF and PGD.

The question facing the government and the scientific community is whether and how germline modification can be introduced in a way that takes account of, and does justice to, the range of different objectives and social values at stake (reduce suffering, equality, justice, respect for diversity and reproductive autonomy).²¹⁰ This question can only be answered in dialogue with the various groups in society.

5.4 Conclusions to Chapter 5

Developments in germline modification raise issues for government, science and society, irrespective of the prospects of the technique becoming clinically available in the Netherlands or elsewhere.

In the short term, the most important issue for the government concerns expanding the possibilities for research on human embryos. In the longer term, should the prohibition of germline modification be lifted to permit clinical applications? If parliament decides to do this, the existing regulatory framework for PGD could initially also be used for germline modification. If it is decided that human germline modification is not acceptable in the Netherlands, the government must be prepared for medical tourism.

Reflection, opinion-forming, public participation and consultation are essential in determining whether or not publicly acceptable and legitimate applications of germline modification are possible and, if so, what procedures for their use should be introduced. The responsibility for this important process lies with the government.

Scientists and medical professionals have a primary responsibility to their patients to ensure that any new medical treatments they receive are both safe and appropriate. Their input to the discussion on the acceptability of tasks is therefore indispensable. However, within the scientific community and the medical professions there are a number of very different views about germline modification and other modern reproductive techniques, and so critical reflection by medical professionals is needed. Wider civil society involvement is also desirable, which makes the dialogue with society so important. The ultimate aim is to prevent the direction of developments being determined by just one or more stakeholder groups.

COGEM and the Health Council of the Netherlands draw attention to the importance of including this issue in the training and continuing education of medical scientists and professionals. If clinical applications of germline modification are permitted and become available, the question is how prospective parents can be properly informed about the method, the alternatives, and possible uncertainties and risks. Society is not a homogenous whole and neither is public opinion, which is why it makes sense to question groups of stakeholders and interested parties, both together and separately. This will prevent important subtleties, distinctions and details in the arguments from being lost in the discussion.

If creating embryos for research purposes is permitted, it will be important to clearly inform donors of gametes about the difference between surplus and cultured embryos, because opinions differ on the distinction between the two.

6. Observations and advice

Germline modification consists of making targeted changes in the genome of cells that make up the germline. This report is about making modifications in the genome of human embryos. Technologies based on CRISPR offer new possibilities for modifying the genome of embryos that avoid some of the technical objections to previous techniques, but at the same they bring the ethical and legal issues surrounding the technique into sharper focus.

Germline modification using CRISPR gene-editing technology is continually evolving

Regarding developments in the science and technology of CRISPR, COGEM and the Health Council of the Netherlands make the following observations:

1. Germline modification using CRISPR gene-editing technology offers possibilities to prevent genetic disorders by repairing a genetic defect in the embryo. These changes are passed on to future generations.
2. At the moment, the technique has the greatest potential for correcting monogenic disorders in which the genetic abnormality is in a single gene or at a single locus on the DNA.
3. For the time being, germline modification cannot be used to repair polygenic disorders because these are caused by errors in multiple genes and have complex hereditary patterns. This also applies to gene-editing techniques for human enhancement.
4. If clinical applications of germline modification are considered desirable and acceptable, further scientific research will be needed into the effectiveness, accuracy and safety of gene-editing techniques. This will require research involving human embryos.
5. It must be emphasised that it will never be possible to obtain absolute certainty about the risks and safety of the technique. The acceptability or otherwise of a risk is not just a scientific question, but a political and social one as well.

Early dialogue with civil society on germline modification

Regarding governance, COGEM and the Health Council of the Netherlands make the following observations:

6. A responsible application of human germline modification requires the active participation of government, science and society, focusing on the choices to be made, who decides what and when, and on the basis of what arguments. An important first step is to develop arguments and values, with input from a dialogue with civil society.
7. Moreover, it is not always possible to make a clear distinction between healthy and defective genes and this has consequences for the discussion about the dividing lines between prevention, treatment and human enhancement. A dialogue on the significance and boundaries of these concepts is essential before decisions can be made on the conditions which should apply to any future clinical applications of germline modification.
8. If it is decided that human germline modification is not acceptable in the Netherlands, the current regulatory framework can be retained. The government must then be pre-

- pared for medical tourism. If the legislature decides to lift the prohibition on germline modification, the existing regulatory framework for embryo selection could initially also be used as a basis for a regulatory system for germline modification.
9. The differences in national legislation on research involving human embryos raise questions about the legal position and protection of researchers in an international context and about the responsibilities of scientific journals.
 10. There are also a number of very different views about the acceptability and safety of germline modification and other modern reproductive techniques within the scientific community and medical professions. Critical reflection by medical professionals and communication with society is therefore crucial.
 11. The consequences and impact of germline modification will initially be very limited and affect only those directly involved (patients and prospective parents with a genetic disorder). However, the effects of germline modification are transmitted to subsequent generations. It is therefore crucial that other interested parties (scientists, medical professionals and the wider public) take part in the dialogue on the desirability and acceptability of these developments.
 12. Clinical applications of germline modification using the CRISPR-Cas gene-editing technology are still a long way off. Nevertheless, the government, the scientific community and society at large will have to start thinking about the implications of this technology now to ensure that ethical and social considerations are not just 'bolted on' when clinical applications become available. This dialogue should pay greater attention to the changing definitions of disease and health (the distinction between prevention, therapy and enhancement), the donation of body tissue, the uses of cultured and surplus embryos, and social justice.

Permitting the use of cultured embryos for research into germline modification

Regarding the legislative framework, COGEM and the Health Council of the Netherlands make the following observations:

13. In the Netherlands it is currently permitted, under certain strict conditions, to carry out research on surplus human embryos. Carrying out scientific research on cultured embryos is prohibited.
14. Making changes to the DNA of an embryo is permitted under certain conditions, as long as no pregnancy results. Cell nuclear transfer is permitted in the Netherlands for reproductive purposes when prospective parents have mutations in their mitochondrial DNA.
15. The government is currently preparing changes to the legislation to make it possible to carry out scientific research on embryos created specifically for this purpose, under strict conditions and for certain research objectives only.
16. The Netherlands is currently not a party to any convention or treaty that could stand in the way of revising Dutch legislation to make it legal to conduct scientific research into germline modification using surplus and cultured embryos.
17. The Health Council of the Netherlands does not consider germline modification and cell nuclear transfer to be fundamentally different. The Council is of the opinion that neither altering mitochondrial DNA to prevent mitochondrial diseases nor germline modification to prevent serious genetic diseases violate human dignity. As long as the technique

is safe, replacing unhealthy genes with healthy ones does not prejudice the interests of the future persons, but rather serves them.

18. The Health Council of the Netherlands advises rescinding the temporary prohibition on creating embryos for important scientific research, in line with the intention of the law. This would make it possible in the Netherlands to conduct scientific research on cultured embryos under strict conditions and for certain research purposes. In this respect, the Health Council of the Netherlands considers fundamental research into the use of gene-editing technologies important enough to justify the use of such embryos.
19. To ensure that both the medical and scientific communities and the general public remain involved in the further decision-making on the use of germline genetic modification, the lifting of the prohibition on scientific research on cultured embryos should be conditional upon the above-mentioned dialogue with scientists, practitioners and the wider public.

This joint report by the Health Council of the Netherlands and COGEM is an initial exploration of the scientific, legal and ethical implications of germline modification using CRISPR gene-editing technology. It is intended to help the government determine its position in the international debate about germline modification. Given the rapid pace and international character of scientific developments in the field of CRISPR technologies, the Health Council of the Netherlands and COGEM recommend that the government carefully monitors developments and where necessary ensures this report is kept up to date.

Abbreviations used

ART	Assisted reproduction techniques
Bp	Base pair (see glossary)
COGEM	The Netherlands Commission on Genetic Modification
<u>CRISPR</u> -Cas	Clustered regularly interspaced short palindromic repeats
CRISPR- <u>Cas</u>	CRISPR associated system
DNA	Deoxyribonucleic acid
ECHR	European Convention on Human Rights
IVF	In vitro fertilisation
MRT	Mitochondrial replacement therapy
NIPT	Non-invasive prenatal testing
PGD	Pre-implantation genetic diagnosis
SSC	Spermatogonial stem cell
RNA	Ribonucleic Acid
WMO	Medical Research (Human Subject) Act (<i>Wet medisch-wetenschappelijk onderzoek met mensen</i>)

Glossary

Allele	A variant form of a gene (e.g. for eye colour of blood group). Alleles may be homozygous (two of the same alleles) or heterozygous (two different alleles).
Autosomal	Traits associated with autosomes – all chromosomes with the exception of the sex chromosomes X and Y.
Bp	DNA consists of base pairs (A–T and G–C); 1,000 base pairs (bp) = 1 kilo base pair (kb); 1,000,000 bp = 1 mega base pair (Mbp).
Chromosome	Chromosomes contain the genetic material and consist of DNA molecules wrapped around structural proteins (histones). The sex chromosomes X and Y determine the sex of the individual: men have an X and a Y chromosome and women have two X chromosomes.
Dominant	A genetic trait is dominant when a single copy of the two alleles is sufficient to express the trait.
Embryo	Cell or cluster of cells with the potential to develop into a human being.
Fetus	An embryo in a pregnant woman's uterus.
Gene editing	The term used for various new techniques for accurately making changes to DNA.
Genome	The total amount of genetic material in a cell, including the genes (coding regions), the non-coding DNA and the genetic material of the mitochondria.
Genotype	The genetic make-up (DNA sequence) of a cell, coded in A, T, G and C.
Heterozygous	Refers to cells that contain two different alleles of a gene.
Homozygous	Refers to cells that contain two identical alleles of a gene.
In vitro	In the laboratory, outside the body.
In vivo	In a living organism.
Mitochondrion	Cell organelle that acts as the power plant of a eukaryotic cell. These cell organelles contain their own DNA, which makes up about 0.1% of all the DNA in a cell.
Monogenic	A trait that is genetically determined by a single gene in the DNA.
Mosaicism	An effect that can occur when a germline modification technique is applied to a multicellular embryo as a result of which some of the cells have the desired genetic modification and others do not.
Ooplasmic transfer	A medical technique in which cytoplasm (the fluid in the cell) from a donor cell is injected into an egg.
Phenotype	The composite of an organism's observable traits or characteristics. The phenotype results from the expression of the organism's genetic code in combination with environmental factors.
Point mutation	A mutation consisting of a single nucleotide change.
Polygenic	A trait that is genetically determined by alleles at different gene loci on chromosomes.

Pronuclear transfer	A medical technique in which the cell nucleus is taken from one cell and placed in another cell from which the nucleus has been removed.
Recessive	A genetic trait is recessive when two identical copies of an allele are needed to express the trait.
Somatic	Somatic cells are all the cells in the body with the exception of the gametes (ova and sperm).
SSC transplantation	A medical technique in which spermatogonial stem cells (from a donor or prospective natural father) are transplanted.
Surplus embryo	Unused embryo from an in vitro fertilisation treatment
Zygote	A fertilised egg

Appendix 1: Committees and consulted experts

Subcommittee on Ethical and Societal Aspects (COGEM)

Professor H.F.M. te Molder (chair)
 Drs. H. van den Berg
 Dr S. van der Burg
 Professor R.A.M Fouchier
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 Professor S. Roeser
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 Professor P. Struik
 Dr J.A.A. Swart
 Ir. H.C. de Vriend
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 Professor J.J.M. Dons (until Sept 16)
 Professor M.J.A. Margadant (until Sept 16)
 Dr V. Beekman (until Jan 17)

* the topic report was prepared by the COGEM Subcommittee on Ethics and Societal Aspects and reviewed and adopted by all COGEM members in the plenary meeting held on 17 February 2017.

Permanent Committee on Ethics and Law (Health Council of the Netherlands)

Professor M.H.N. Schermer (chair)
 Dr E.C.A. Asscher (secretary)
 Mr. A.C. de Die
 Mr. dr J.H.H.M. Dorscheidt
 Professor G.A. den Hartogh
 Mr. dr R.E. van Hellemond (secretary)
 Professor A.C. Hendriks
 Professor K. Horstman
 Professor C. Leget
 Mr. dr M.C. Ploem
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Consulted experts

Professor A.L. Bredenoord

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Professor R.C. Hoeben (COGEM)

Professor S. Repping

Mr. C. Schoonderbeek

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