

Discussing the modification of heritable DNA in embryos

Lessons for a public dialogue



Authors

Sophie van Baalen, Jeroen Gouman and Petra Verhoef

Cover photo

Co de Kruijf / Hollandse Hoogte

Illustrations

Laura Marienus / Rathenau Institute

Preferred citation:

Baalen, S. van, J. Gouman and P. Verhoef (2019). *Discussion of the modification of heritable DNA in embryos*. The Hague: Rathenau Instituut

Foreword

Genetically modified twins, Lulu and Nana, were born at the end of 2018, even though genetic modification of humans is prohibited under existing legislation, even in China. Researcher He Jiankui had nevertheless used the new CRISPR-Cas9 technology in the lab to alter a heritable gene in the babies when they were embryos – a procedure known as germline genome editing.

This genetic modification of humans raises many ethical, moral and practical issues. How do we feel about it? Would permitting it for medical purposes create hope that heritable diseases could be eradicated? Can we make that decision for future generations? Where do the boundaries of what we regard as acceptable lie?

Eleven organisations, including the Rathenau Institute, decided to organise a public dialogue on these questions. In this report, based on desk research and a scenario workshop, we discuss the historical and international contexts, the dialogue to date and relevant social and ethical considerations.

The debate about modifying heritable DNA in humans is part of a wider discussion about how far we are prepared to go with biotechnological advances. Do we understand the consequences and risks of new technologies? How do they alter our view of what constitutes a good and healthy life, and the limits to it? Every technological development has its own characteristics, but all raise similar questions.

Under the theme ‘Making perfect lives’, we have long been researching developments relating to embryo research, human-animal hybrids and germline genome editing. This research has repeatedly demonstrated that the pursuit of a perfect life also makes people vulnerable.

To ensure that different perspectives and values are taken into account in the public and political debate regarding human genome editing, here we review the most important considerations and arguments. This report contains ten lessons for the content and shape of a broad public dialogue on the subject because it is essential, in the interests of current and future generations, that we conduct this dialogue very carefully, and together. Starting in October 2019, everyone will be able to join in the debate at meetings throughout the country.

Melanie Peters

Director, Rathenau Institute

Summary

Advances in biomedical science and technology allow us to diagnose, treat or prevent a growing number of disorders. The expanding knowledge of the genetic basis of human traits and disorders and new technologies for modifying genes could in time make it possible to alter the building blocks of our lives: human DNA. That could have a variety of social repercussions – changes that affect us all and which, as we show in this report, we need to discuss.

We speak of *germline genome editing* when the DNA in the cells of a human embryo, or in cells that could grow into reproductive cells, or in a recently fertilised human egg cell (the very early stage of an embryo) is modified in de lab. If such a genetically modified embryo grows into a child after being transferred to the womb, the DNA of that child's offspring will also contain these modifications. In the Netherlands, making these types of alterations in human germline cells with the intention of creating a viable foetus and pregnancy is prohibited by Article 24(g) of the Embryo Act. This ban is based not only on the uncertainty surrounding the safety and effectiveness of the technology but also on ethical and societal considerations. In the coalition agreement, the current government stated that there should first be a public dialogue on the issue of research with human embryos and the modification of heritable DNA before any decision was made on whether to amend the Embryo Act.

In 2012, a new technology was discovered for modifying DNA: CRISPR-Cas9. In contrast to earlier genome-editing technologies, CRISPR is often referred to as a 'molecular scissors'. Scientists regard the technology as 'easy to use, precise and relatively inexpensive'. The discovery appears to create new possibilities for preventing heritable diseases by making targeted genetic modifications in human embryos before they are transferred to the womb. This development has reopened the discussion about the modification of heritable DNA.

Guidelines for a broad public dialogue

In 2018, eleven organisations in the Netherlands, including the Rathenau Institute, took the initiative to organise a broad public dialogue – a process of collective opinion formation – to ascertain the views of Dutch society towards the modification of heritable DNA in the early development of human embryos. The Ministry of Health, Welfare and Sport welcomed this initiative and has, therefore, financed the project entitled 'A public dialogue on germline genome editing'.

This report provides guidelines ('lessons') and instruments (scenarios) for conducting a national dialogue on the subject. In the first part of the report, we describe the debate that has been conducted up to now in the Netherlands – mainly in the media. We review what is already known regarding public opinion on the subject and present an analysis of the reasons for the existing regulation. We also describe the ethical and social issues that play (or could play) a role in the dialogue on the question of whether targeted modification of the genome of future persons is acceptable, and if so, for what purposes and under what conditions. To that end, we examined reports on the subject by national and international advisory bodies and ethics councils and conducted fourteen interviews with representatives of groups and parties with an interest in the dialogue.

Future scenarios

Techno-moral future scenarios can help thinking about and discussing possible futures. In the second part of this report, we, therefore, describe four techno-moral scenarios or foresight studies. These were produced based on the findings from the analyses, a scenario workshop with experts, and two focus groups with non-experts organised by the National Institute for Health and the Environment (RIVM). Based on the scenarios, NEMO Kennislink has produced techno-moral vignettes (in this case, animations) to facilitate a discussion on the social implications of the use of germline genome editing.

Four future scenarios have been formulated based on two key uncertainties (the culture surrounding reproduction and pregnancy and advances in technology):

- 1. Disease prevention by germline genome editing**
- 2. Modification of heritable human DNA in a free reproduction market**
- 3. Genetically-related children for everyone**
- 4. No modification of the heritable DNA in embryos as a precautionary measure**

The debate in the Netherlands

In the media in the last few years, various experts have advocated reopening the debate about the acceptability and desirability of human genome editing. We discern two approaches in that discussion. In the first, the emphasis is on the direct consequences ('usefulness and necessity') of the technologies, and manipulation of the DNA of future persons is seen as a potentially valuable medical intervention for preventing heritable disorders. The alternative approach focuses on the wider implications of the targeted modification of the human genome for individuals, society, and mankind.

There have been a few surveys of public attitudes towards human genome editing in the Netherlands and abroad. They often reveal a similar pattern. Modification of the genetic characteristics of offspring is regarded as controversial and acceptance of it depends on the proposed application. Preventing heritable disorders is regarded as acceptable more often than enhancing human traits. Although insights from articles and public surveys could contribute to a dialogue, no broad public debate is yet being conducted on the subject in the Netherlands.

Dialogue with different levels and dimensions

There is still a lot of uncertainty surrounding scientific and technological developments that enable the modification of heritable human DNA, including its safety and the consequences for individuals and society as a whole. These uncertainties will not be easily resolved and need to be thoroughly explored.

To provide a systematic overview of the social and ethical issues involved, we have divided them into three domains: *research in the laboratory*, *research with humans* and *application in practice*. It is important to cover the issues arising in each of these domains in the dialogue. In turn, different questions, considerations and issues can arise at different levels within each domain: the *instrumental*, the *societal* and the *global* (international) level. The time dimension is also relevant: these issues not only concern the here and now, but also future generations and future societies.

Conditions for conducting a public dialogue

Based on the analysis of the public debate in the Netherlands up to now, the relevant ethical and social issues and the Rathenau Institute's years of experience with conducting public dialogues on (emerging) technologies, we start by formulating some general requirements for a national public dialogue:

- **Public engagement**

It is essential to devote a lot of attention to reaching and engaging members of the public so that they can inform themselves, form an opinion and discuss different perspectives and arguments.

- **Information about the wider consequences for individuals, society, and humanity**

The dialogue must promote deep, joint consideration of the wider social consequences of the introduction of new technologies. Members of the public must also be informed of potential consequences, for themselves and others, for society as a whole and for current and future generations.

- **Clarity about the subject matter of the dialogue**

There is no consensus on what precisely is being discussed in a debate on the modification of hereditary DNA of future persons: the development of new medical treatments that could prevent a lot of suffering, or the future, dignity, and identity of individuals and humanity. Consequently, there is also (implicit) disagreement on what the central issues of the dialogue should be. Members of the public need to be able and enabled to speak out on both the desirability of germline genome editing and the conditions under which it can be permitted.
- **Involvement of related themes**

Because the theme of human genome editing is closely related to other themes, such as scientific research with human embryos, embryo selection, prenatal diagnosis, and genetic screening, issues relating to these connected themes could also arise in the dialogue.
- **Different participants, different roles**

These points call for a different role in the dialogue for experts in medical science and for input from experts from other fields, in addition to the input of parties that are directly or indirectly involved.
- **Combination of methods**

A mix of methods will need to be used to achieve the goal of public dialogue. Scientific public surveys provide insight into the attitudes and considerations of only a small number of participants. Other activities and initiatives are needed to reach a wider audience.

Ten lessons for the dialogue on germline genome editing

Organising a successful dialogue on germline genome editing presents challenges in terms of both its content and its form. The general conditions set out above lead to the ten following lessons conducting the dialogue on the modification of heritable DNA in human embryos.

Lessons for the content:

1. The questions of 'whether' and 'how' are interlinked – the dialogue should, therefore, not be limited to one or the other.
2. Include the question of what is at stake in the dialogue.
3. Clearly explain what is needed to make use of human germline genome editing (the research trajectory and basic conditions for the use of the technology in practice).
4. Discuss the broader implications of the targeted editing of the human genome for the individual, society, and humanity.

5. Turn it around: think about the society of the future – what its core values should be and what role modification of heritable DNA in humans could play in that respect.

Lessons for the form:

6. Organise a dialogue not only between groups of stakeholders and interested parties, but also amongst themselves.
7. Actively seek ways of reaching and informing less accessible groups and engaging them in the dialogue.
8. A dialogue is not a platform for exchanging fixed views.
9. Involve and instruct appropriate experts and people with practical experience.
10. Think carefully about the themes, the material, the terminology and the subject matter that will be discussed during the sessions.

Contents

Foreword	3
Summary	4
Introduction.....	12
Part I: Research for the lessons.....	19
1 Modification of hereditary DNA in context.....	20
1.1 Converging technologies	20
1.2 History, mechanics and application of genome-editing technology.....	26
1.3 Discussions about new technologies at different levels.....	31
1.4 History of national and international laws and regulations on germline genome editing.....	32
1.5 The importance of a broad discussion	35
1.6 Summary: points of departure for a public dialogue	36
2 The discussion so far	37
2.1 The reasoning behind laws and regulations	37
2.1.1 National regulation.....	37
2.1.2 International regulation and treaties.....	39
2.1.3 Summary: a mix of pragmatic and fundamental considerations	39
2.2 The (public) debate about germline genome editing	40
2.2.1 Utility and necessity of germline genome editing.....	41
2.2.2 Wider consequences for individuals, society, and humanity ..	43
2.2.3 Similarities with earlier discussions	44
2.2.4 Distinctions between desirable and undesirable applications	45
2.2.5 The discussion about research with embryos	45
2.2.6 Complexity of the international context.....	46
2.2.7 Summary: little agreement in the public debate	47
2.3 Public opinion research into the modification of heritable DNA	48
2.3.1 Public opinion research in the Netherlands	48
2.3.2 Public surveys in other countries	50
2.4 Conclusion: from a narrow discussion to a broad public dialogue	51

3	Social and ethical issues of germline genome editing	53
3.1	Questions in three domains	54
3.2	Domain of research in the laboratory	55
3.2.1	Considerations relating to the creation of embryos for research	55
3.2.2	Safety and effectiveness of laboratory research	57
3.2.3	Summary: the dialogue is about research in the laboratory	58
3.3	Domain of research with humans	58
3.3.1	Weighing uncertain risks against uncertain benefits	58
3.3.2	Considerations for precautionary measures.....	59
3.3.3	Research in an international context.....	60
3.3.4	Summary: the dialogue on human genome editing must also address research into the modification of DNA of future persons	61
3.4	Domain of application in practice	62
3.4.1	Interpretation of terms used in the context of genome editing	62
3.4.2	Importance of prior knowledge of a person’s genetic predisposition	63
3.4.3	Uncertainty about genetic modification with genome-editing technologies	65
3.4.4	The distinction between desirable and undesirable applications of germline genome editing.....	68
3.4.5	Considerations relating to ethical principles and concepts such as human dignity and identity	72
3.4.6	The impact on future generations.....	74
3.4.7	Attention for the broader public and social consequences	75
3.4.8	Summary: the role of broader social consequences in the dialogue on germline genome editing	78
3.5	Conclusion: dialogue with many levels and dimensions	79
4	Lessons for holding a public dialogue	82
4.1	Requirements for a public dialogue.....	83
4.2	Lessons for the dialogue on germline genome editing.....	86
4.2.1	Lessons for the content of the dialogue.....	86
4.2.2	Lessons for the form of the dialogue.....	89
4.3	Conclusion.....	91
	Part 2: Future scenarios	93
5	Future scenarios - the modification of heritable DNA	94
5.1	Four future scenarios.....	96
5.1.1	Scenario 1.....	96

5.1.2	Scenario 2.....	102
5.1.3	Scenario 3.....	109
5.1.4	Scenario 4.....	114
Bibliography – Part I		120
List of newspaper articles consulted.....		129
Bibliography – Part II		134
Appendix 1: List of interviewees.....		139
Appendix 2: Participants in scenario workshop		140
Appendix 3: The methodology of the future scenarios		141

Introduction

We have become steadily healthier over the last few decades: we are living longer and remaining healthy longer. Advances in biomedical science and technology have made a significant contribution to this trend; our expanding knowledge enables us to diagnose and treat or prevent a growing number of diseases and disorders. With biomedical technology, we can also intervene ever more deeply in human lives (Van Est et al., 2014). Greater knowledge of the genetic basis of human traits, characteristics and disorders now also makes it possible for scientists and physicians to manipulate the building blocks of life, our DNA. But making changes in heritable human DNA can have consequences for society – consequences that affect us all and are, as we show in this report, important to discuss.

From 1953, when the 3D structure of DNA (the molecule that codes for the properties and traits of cells, tissue, and organs) was discovered, scientists tried to unravel the *sequence* of this code. In 2003, this was accomplished when, after years of research, the Human Genome Project (HGP) mapped the sequence of the human genome, the complete set of DNA that exists in the core of every cell in the human body.¹

In addition to techniques with which the sequence of DNA can be *established*, other techniques are now also being developed with which the sequence of DNA can be *modified*. With these techniques comes the promise that it will be possible to remove undesirable genetic traits from the DNA. The treatment of a heritable disease by modifying the DNA in a person's cells (the DNA of cells in the lung, for example) is known as *somatic gene therapy*. A lot of research is currently being conducted into this form of gene therapy, which has in some cases been used on patients.

The latest development in the technology of *genome editing*, the modification of heritable human DNA, is CRISPR-Cas9 (Cong et al., 2013 and Mali et al., 2013).² Because CRISPR-Cas9 is often regarded as 'easy to use, precise and inexpensive' compared with previous technologies (Travis, 2015), many scientists see it as very promising. In technical terms, restoring physical functions by making changes in genes in a targeted, precise and cost-effective manner seems close to becoming a

1 See www.genome.gov/human-genome-project

2 CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats; Cas9 for CRISPR associated protein 9.

realistic option (European Group on Ethics in Science and New Technologies, 2019). In this way, inherited diseases could be cured by removing the genetic basis for the disorder in the affected cells and tissue.

Genome-editing technologies can, therefore, lead to new treatments for *living* persons. In theory, they can also be used to remove the genetic predisposition to heritable diseases from the DNA of *future persons*. This requires genetic modifications to be made at the earliest stage of development of an embryo: in a recently fertilised egg or an embryo that only consists of a few cells. If the genetically modified cells of this embryo multiply, and the embryo grows into a human, those genetic modifications will be part of that person's cells. Because the change is now part of that person's genome, it will also be carried by the reproductive cells (sperm and egg), so that genetic changes during procreation are passed on to his or her children (and the children of those children, and all subsequent generations). This is known as *germline genome editing*. The germline is the name for all cells that can grow into reproductive cells, and, therefore, contain the heritable DNA that is passed on to one's descendants during procreation.

Legislation and regulation

The CRISPR-Cas9 technology was only discovered in 2012,³ but other, less efficient genome-editing technologies available were already available (Maxmen & Mallet, 2015). The possibility of modifying the genetic properties of future persons had, therefore, been foreseen in ethical debates and the public imagination for decades. The fact that the consequences of modifying the genetic properties of future generations can be far-reaching is reflected in national and international legislation and regulatory regimes, which differ greatly from one country to another. In most countries, including the Netherlands and the rest of the European Union, establishing a pregnancy with reproductive cells or embryos whose heritable DNA has been altered is prohibited. Genetic modification of the germline is also restricted in various human rights conventions (UNESCO, 1997; Council of Europe, 1997a). Although regulation of the technology and reflection on the medical and ethical issues develop in an international context, there are still big differences between the rules of different countries (Ledford, 2015). And individual researchers also sometimes reject existing legislation and the prevailing consensus.

One of these is the Chinese researcher He Jiankui, who announced in November 2018 that twin girls had been born using an IVF treatment during which he modified one of their genes in the laboratory – during the early embryonic phase (Regalado, 2018). He asserted that the change had made the babies HIV-resistant.

3 See www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline.

There are numerous interests and stakeholders involved in the debate about new genome-editing technologies to modify embryonic DNA: research in this field could yield important scientific insights; the technologies could also be a welcome addition to the ‘toolkit’ of specialists in reproductive medicine, which is now a multi-billion-dollar industry; the technologies also provide hope for carriers of serious, heritable diseases that they could have a healthy child by preventing the disease from being passed on to their offspring.

The situation in the Netherlands

In the Netherlands, the modification of heritable DNA in human embryos is regulated in the Embryo Act, which prohibits the inducement of a pregnancy using reproductive cells or embryos whose DNA has been altered (Embryo Act, art. 24(g)) and the creation of embryos specifically for research (Embryo Act, art. 24 (a)). In its coalition agreement, the present Dutch cabinet stated that there should be a public dialogue on important medical-ethical issues before any decision is made about amending the Embryo Act: *‘A separate issue is that of research involving embryos and the possibility of changing an embryo’s DNA (germline genome editing)’* (Rijksoverheid, 2017 p. 18)⁴. Several scientific institutes and advisory councils in the Netherlands (COGEM & Health Council, 2017; COGEM, 2019a; KNAW, 2016) have recently advocated lifting the ban on the creation of human embryos specifically for scientific research. That would allow not only fertilisation to occur in a laboratory for research purposes, but also – among other things – research into modifying heritable DNA at a very early stage of an embryo’s development. In their statements and reports, these bodies also called for a public dialogue on the use of germline genome editing, to alter heritable DNA. In a letter to the House of Representatives in 2018, the Minister of Health, Welfare and Sport expressed the desire for a broad discussion that leaves room for the expression of different perspectives and nuances (Kamerstukken II 2017/2018, 34 990, no. 1). In this way, political decision-making would be guided by society through public opinion.

Initiative for public dialogue on germline genome editing

At the end of 2018, a number of organisations in the Netherlands, persuaded of the need for a wider debate, took up the challenge and together started to organise a broad, high-profile public dialogue on the desirability and possible applications of germline genome editing in human embryos.⁵ Minister of Health, Welfare and Sport Hugo de Jonge welcomed the initiative and his ministry granted a subsidy for the

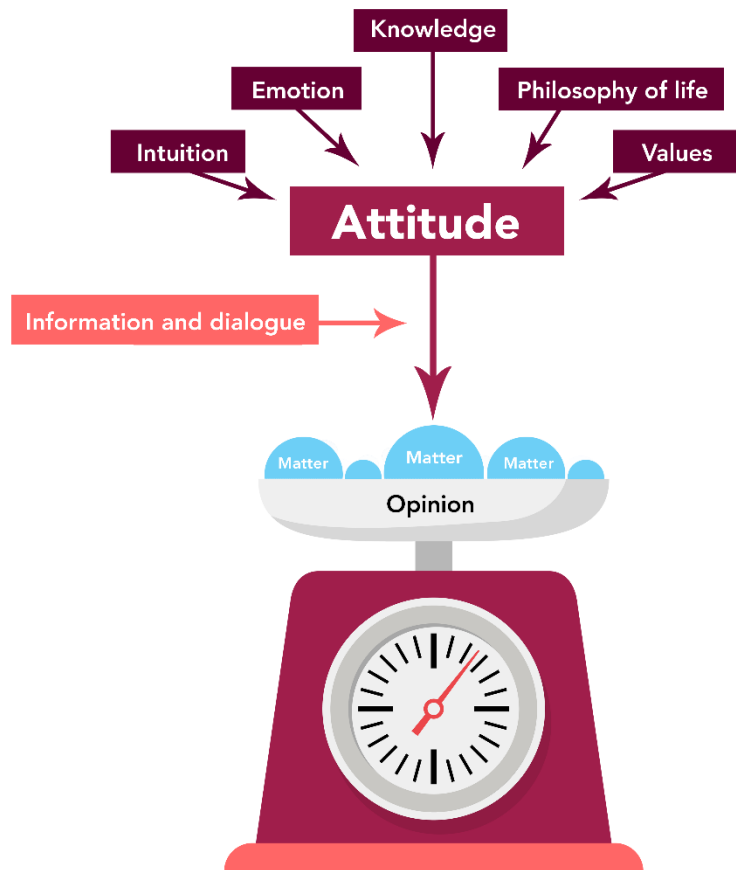
⁴ *“Ook is aparte aandacht nodig voor het vraagstuk van onderzoek met embryo’s en de mogelijkheid DNA van embryo’s te veranderen (kiembaanmodificatie).”*

⁵ The project is an initiative of Erfocentrum, Erasmus MC, Rathenau Institute, NPV Zorg voor het Leven and NEMO Kennislink. Erfocentrum is coordinating the project. Various other organisations are partners in the project and are organising activities for it: Amsterdam UMC, the Center for Media and Health, the Dutch Association for Community Genetics and Genomics (NACGG), the National Institute for Public Health and the Environment (RIVM), the Dutch Clinical Genetics Society (VKGN) and the Dutch Parents and Patients Alliance for Rare and Genetic Diseases (VSOP).

two-year project 'A national dialogue on germline genome editing' at the end of 2018. The project commenced in early January 2019 to facilitate and promote a process of collective opinion formation in the form of a broad public dialogue. For this project, it will be necessary to reach and inform a wide audience and encourage them to discuss their hopes, wishes and concerns regarding the modification of heritable DNA in human embryos, and its broader social consequences. Figure 1 provides a diagrammatic representation of this collective opinion formation process.

This report provides a manual for the broad public dialogue, based on recent research by the Rathenau Institute and its previous experience. The results and findings from the public dialogue will be collected in a final report at the end of 2020 to inform political decision-making and policy formulation. The results will also be made available in an accessible form for a wider public.

Figure 1 Weighing of various issues in the dialogue



What is the weight of personal considerations?

In the course of the public dialogue, participants will converse with each other to form an opinion about the modification of heritable human DNA. They will start the dialogue with a basic attitude, which is dictated by their personal knowledge, intuitions, emotions, beliefs and values. During the dialogue, they will receive more information about the subject and the issues involved. In addition, various initiatives and activities will be facilitated and stimulated to promote discussion of those issues, thus prompting an exchange of diverse considerations, arguments, expectations and perspectives. In the process, everyone will be able to at least start to form a personal opinion, which will depend on the weight they attach to the various issues. Source: Rathenau Institute

Experience with similar dialogues

Experience with other public dialogues on new technology in the Netherlands, such as the debates on nanotechnology and nuclear energy (Hanssen, Walhout & Van Est, 2008; De Vries et al., 2015), has taught us that it is not easy to conduct such a dialogue. Earlier public dialogues were often based on the premise that merely

informing the public about the opportunities and risks of the application of new technologies was sufficient to provide a reliable introduction to the subject.

We now know that this is not enough to enable members of the public to arrive at an informed opinion: they must also be informed about the societal aspects of the technology. And we also now know that a public dialogue on a particular issue often rekindles the discussion of other issues.

For example, closely connected with the dialogue on DNA modification is the issue of creating human embryos (the process of fertilisation) in the laboratory for research purposes, which could help research into the safety and effectiveness of genome editing in human embryos. Research has been done with animal embryos, but biological differences mean that they do not always provide useful insights concerning humans. Residual embryos – embryos that remain after an *in vitro* fertilisation (IVF) treatment and which may be used for research – are already several days old and the cells have already separated several times. As a result, according to scientists, they are unsuitable for this type of research. In that context, it has to be noted that research into genome editing is not the sole reason for calls to permit the creation of human embryos. They could also provide important insights into the early development of life from the moment of fertilisation, knowledge that could help to improve IVF treatments and prevent miscarriages.

Altering, deactivating or removing the genes of human embryos or reproductive cells can provide scientists with valuable knowledge about the role these genes play in processes such as the fertilisation of an egg, the normal versus abnormal development of an embryo and the origin of diseases. However, the use of human embryos specifically for research has long been a controversial subject. Opinions about the scientific research required before genome-editing technologies can be used for medical applications of DNA modification will, therefore, also play a role in the public dialogue.⁶

Guidelines for a public dialogue

This report was written in preparation for and as a guide to the public dialogue on modification of heritable DNA in future persons (germline genome editing), which formally commenced in the Netherlands in October 2019. The first part of the report describes research that yields some guidelines ('lessons') for ensuring that the dialogue proceeds smoothly.

6 The Ministry of Health, Welfare and Sport has commissioned a public dialogue on 'the creation of embryos specifically for research' at the same time as the project 'National dialogue on germline genome editing'. The public dialogue will be conducted from June 2019 until the end of May 2020.

Chapter 1 briefly outlines the historical context, of both the technological developments and the political and ethical discussion, as well as the most important international developments. Chapter 2 describes research that has been conducted on public opinion, the motives for existing regulation and the ongoing debate between various stakeholders in the media, particularly in the Netherlands, but also elsewhere. Chapter 3 provides an overview of the social and ethical issues raised in the debate on the modification of heritable DNA in human embryos and future generations. Chapter 4 uses the insights from the preceding chapters to present ten lessons for the public dialogue. The second part of the report contains four techno-moral future scenarios, or foresight studies, based on (1) the findings from part 1, (2) a scenario workshop with experts, and (3 and 4) two focus groups with non-experts.⁷ Scenarios can help shape thinking about and discussion of possible and uncertain futures, but are not intended to predict the future. On the basis of the scenarios, techno-moral vignettes⁸ have been drafted to support the discussion of the possible societal consequences of the use of germline genome editing.

This report is designed to support the public dialogue on the modification of DNA in human embryos and future generations in the Netherlands and hence provide insight into how Dutch citizens think about germline genome editing and the values and considerations that play a role in the debate. At the same time, it provides an overview of the current state of affairs concerning the societal aspects of human genome editing. Accordingly, it serves as a source of information for both professionals and interested persons.

7 The focus groups were organised in June 2019 by the RIVM, which is publishing a separate report on them.

8 Techno-moral vignettes are short, appealing scenes (in the form of an animation, for example) set in the world of the scenario, for example from the perspective of a couple that would like to have a child. These vignettes can be used in the dialogue to prompt reflection on the ethical aspects of modifying heritable DNA. They will be produced by NEMO KennisLink.

Part I: Research for the lessons

1 Modification of hereditary DNA in context

Since Chinese scientists published a study in 2015 in which they attempted to use CRISPR-Cas9 to modify heritable DNA in human embryos in the laboratory (Liang et al., 2015), the issues surrounding the modification of human embryonic DNA and future generations have been the subject of fierce debate (again). However, the political and ethical discussion of the subject has been underway for far longer and has an extensive historical context. Whereas it is sometimes argued that ethical thinking lags behind technological developments and is only able to *respond* to them, in the case of technologies for human genome editing, the possibility of manipulating the genetic properties of humans has been *anticipated* for decades (Van Est et al., 2017). This chapter provides an overview of the history of both the technological developments that affect human genome editing and the political and ethical discussion that has been conducted on the subject. It places the subject in a broader context of *technology assessment* and describes international developments. Finally, this chapter provides insight into how human genome editing has been *framed* in the debate on the subject up to now.

1.1 Converging technologies

Modern biotechnology and developments in digitisation, have given the impression that the human body can be measured, analysed and made perfect (Van Keulen & Van Est, 2018). Modifying the genes of offspring fits into that trend. Since the use of *in vitro* fertilisation (IVF), embryos no longer exist solely within the human body. Human life can be created in a controlled laboratory environment by fertilising a human egg in the lab – *in vitro* – with human sperm. Besides giving prospective parents who have difficulty conceiving the chance to have a child that is at least partially genetically related, IVF made it possible for the first time for scientists to see and manipulate the first steps of human life. The early human embryo thus became a possible object of observation, research and assessment (Jasanoff, 2019). For example, IVF physicians assess the viability of embryos on the basis of visual criteria. One or two of the embryos believed to be the most viable are then transferred to the womb. The IVF procedure is described in box 1.

Box 1 IVF treatment

During an IVF treatment⁹ the woman receives hormone injections for a month. The woman's hormone production is suppressed using a subcutaneous injection or a nasal spray. After two or three weeks, the physician starts administering a follicle-stimulating hormone (FSH), which causes multiple eggs to grow in the ovaries instead of a single cell as occurs during a normal fertility cycle (these eggs grow in what are known as follicles). The FSH has to be administered subcutaneously every day with a pen or a needle. During the period when the FSH is being administered, an ultrasound scan is made every day to monitor the growth of the follicles. If they are large enough, another hormone, human chorionic gonadotropin (hCG), is administered to promote the maturation and release of the eggs in the follicles. Within 36 hours the eggs are then removed from the follicles using a method called a follicular puncture. For this procedure, the IVF physician pricks open the mature follicles in the ovaries with a large needle inserted through the wall of the vagina, guided by an ultrasound scan. The follicles with eggs are then aspirated.

The man is asked to provide sperm before or after the follicle puncture. Laboratory staff then check whether there are sufficient rapidly moving sperm cells and how many eggs were acquired (usually between five and ten). These are then collected in a container. The next day, the cells are checked to see whether they have fertilised (the fusion of an egg cell and a sperm cell whereby the genetic material of both parents converges to create a unique genome). Fertilised egg cells that divide are known as embryos. After two to five days, an embryologist examines the quality of each embryo on the basis of its external features under a microscope. One embryo of the right quality is then transferred to the womb using a plastic tube. In exceptional cases – for example, with an older woman or if the available embryos are of poor quality – two embryos are sometimes transferred. Because the woman's hormone balance has been suppressed, she must continue to use hCG after the embryo is transferred to her womb to ensure that the uterine lining is thick enough. Remaining embryos can be frozen to be used later for another treatment if necessary. They can also be donated to science or to another couple.

If there is no fertilisation after two attempted IVF treatments, it might be decided to opt for an IVF treatment combined with intra cytoplasmic sperm injection (ICSI). In this procedure, a single sperm is injected directly into an egg in a petri dish. The embryo that is formed is then transferred to the womb.

The chance of inducing a pregnancy with an IVF treatment is roughly 36.2% per cycle, including pregnancies derived from a frozen embryo. In 2017, there were 13,991 IVF treatments (including ICSI) in the Netherlands, from which 5,067 children were born. In 2017, one in 32 children was born with the help of IVF or ICSI.¹⁰ Research in the Netherlands has shown that IVF children have a slightly lower weight at birth, but that by the age of two there is no difference in their physical and psychological development. IVF treatments are stressful for the woman, who also has a small risk of suffering possibly serious side-effects, such as *overstimulation syndrome* (as a result of hormone treatment), haemorrhaging or an infection (resulting from the follicle puncture).

In 2003, the entire human genetic code was mapped for the first time. Now, seventeen years later, (human) DNA can be read and analysed many times faster and cheaper, due in part to improved *sequencing* techniques and the exponential increase in computing power (Molteni, 2018). Scientists are steadily learning more about the genetic foundations of disorders, and this knowledge can be used – in addition to visual inspection – to test embryos for heritable disorders before they are transferred to the womb with a procedure known as *pre-implantation genetic diagnosis* (PGD; see also box 2). In many countries, including the Netherlands, prospective parents who know that they have a heritable disorder whose location in the DNA is known and can be determined with a test, or that they are carriers of that gene, can use PGD to select an embryo that does not carry the disorder.¹¹ This is known as *embryo selection*.

9 See www.freya.nl/brochures/ivf-in-vitro-fertilisatie.

10 See **Error! Hyperlink reference not valid.**

11 See www.pgdnederland.nl/voor-welke-aandoeningen for a list of disorders for which PGD is used.

Box 2 Embryo selection

In the Netherlands, prospective parents who know that they have a serious heritable disorder or are carriers of the gene that causes that disorder have the option of selecting an embryo without that gene. The procedure for *embryo selection* is similar to the one for an IVF or ICSI treatment, with the additional feature that, with embryo selection, the DNA of the available embryos is examined before an embryo is transferred to the womb (it is therefore also known as *pre-implantation genetic diagnosis*, PGD). After three or four days (when the embryo created with IVF or ICSI consists of approximately eight cells), one or two cells are removed with a thin needle by making a small hole in the membrane of the embryo. These cells are then examined for the presence of the genetic defect that causes the disorder. Before an embryo selection procedure starts, the prospective parents undergo an extensive genetic examination. They are also counselled about their options, usually by a clinical geneticist. As far as known, there are no additional risks for the mother or the future child with embryo selection compared with IVF and ICSI alone. The chance of a successful pregnancy is similar. In 2017, 365 couples started 497 PGD treatments and 132 pregnancies (for longer than three months) resulted.¹²

Thanks to technologies for screening the entire genome at once, more heritable disorders can be diagnosed; accordingly, several genes can be investigated simultaneously. For this reason, in recent years there has been a greater demand for PGD treatment for 'new indications', often rare genetic disorders. In these cases, the PGD working group at Maastricht UMC+ (the only medical centre in the Netherlands where PGD is carried out) decides whether PGD will be applied. In case of doubt, the request is submitted to the PGD National Indications Committee.

12 See https://heritage.azm.nl/Afbeeldingen/ebooks/PGD_Jaarverslag_2017/index.html#8.

The discovery of CRISPR-Cas9 seems to have created a new way of preventing heritable disorders by making targeted genetic modifications to embryos before they are transferred to the womb.

In other words, the new technologies are increasing our knowledge of the genetic foundations of a disease. In combination with faster and less expensive technologies for genetic screening (before and during pregnancy, see box 3) and diagnosis (including PGD), artificial reproductive methods (including IVF) and genome-editing technologies (including CRISPR-Cas9), the possibilities for establishing whether a person is a carrier of a genetic disorder are also expanding. That also means that embryos without a heritable disorder can be selected and that, in the future, it might be possible to modify the DNA of embryos in such a way as to remove the predisposition to a disorder (Van Est et al., 2017).

Box 3 Genome editing and screening during pregnancy

Genome editing

To modify the DNA of an embryo, the embryo has to be created outside the body. In other words, a couple must undergo IVF treatment. To modify DNA, a set of molecules (for example, CRISPR-Cas9) has to be introduced into the nucleus of a cell. These molecules cut the DNA at the right point and repair it correctly. To increase the chance that the DNA of all the cells in an embryo are being modified, this has to be done as early as possible in the embryo's development, when it consists of one or just a few cells. As with PGD, after a few days, when the embryo has divided several times, a cell can be removed to determine whether the DNA in that cell has been successfully modified and that no undesirable modifications have been made.

Screening during pregnancy

The DNA of the foetus can also be examined during pregnancy. With the Non-Invasive Prenatal Test (NIPT), a blood sample is taken from the mother. Because there are also pieces of DNA from the placenta in the mother's blood, the baby's DNA can be examined. In the Netherlands, NIPT is only used to screen for chromosome abnormalities, which occur where there are too many or too few chromosomes or where there is a fault in the structure of the chromosome. In principle, the most common chromosome abnormalities (Down, Edward's or Patau syndrome) are screened for, but couples can also choose to test for so-called secondary findings (less common chromosome abnormalities).

If there is evidence of a chromosome abnormality in the foetus, NIPT is always followed by removing a piece of the placenta (chorionic villus testing) or some amniotic fluid (amniocentesis) through the abdominal cavity with a large needle. These tests are more reliable than the NIPT and are generally used to establish the presence of a chromosome abnormality. But, in contrast to NIPT, they can also be used to test the foetus's DNA for genetic abnormalities and so establish whether an unborn child has a heritable disorder. By then, it is no longer possible to prevent it through embryo selection (or, in the future, with genome editing), but the couple can choose to terminate the pregnancy.

1.2 History, mechanics and application of genome-editing technology

Ever since the discovery of recombinant-DNA technologies in 1972 (Jackson et. al., 1972), with which DNA can be implanted (via a virus) into the genome of a bacterium, research has been conducted into methods of modifying the DNA of bacteria and other organisms, including humans, animals and plants. The challenge with genome-editing technology is to make the desired alteration in the correct position in the DNA and not in other, unintended, locations. Genome-editing technologies, therefore, consist of a set of molecules, some of which are capable of recognising the correct location in the DNA and others that function as molecular scissors, which can cut through the DNA at that location. The DNA is then repaired by the cell itself.

With the first generation of genome-editing technologies,¹³ changes could in principle also be made at a specific location in the DNA. However, a practical problem with those technologies was that a specific new molecule had to be created for each location where the DNA was to be modified (Habets, Van Hove & Van Est, 2019). The CRISPR-Cas9 technology greatly simplifies that process. The molecular scissors, 'Cas9', can cut practically anywhere in the DNA, depending on the guide RNA (a sort of molecular navigation label) to which it is linked. In principle, the discovery of CRISPR-Cas9 makes the process of modifying genes faster, easier, less expensive and more precise. Consequently, the interest in and debate about the use of genome editing for treating or preventing heritable disorders in humans has surfaced again.

13 Technologies such as the meganucleases, zinc finger nucleases (ZFNs), and the transcription activator-like effector nucleases (TALENs).

Box 4 Genes and disease

The human genome is made up of strings of DNA, which contain our genetic code. This code is divided into 23 pairs of chromosomes, each of which includes one chromosome from the father and one from the mother. The chromosomes contain the genes: pieces of genetic code carrying the instructions for producing a protein. There are two variants of each gene (one on each chromosome). Proteins are molecules that play an essential role in the structure and functioning of the human cells that make up every tissue and organ in the human body. A defect in a gene can disrupt the production of the protein associated with that gene. This affects the cellular processes and physical functions in which the protein is involved, thereby causing a disorder. Autosomal recessive disorders only occur if there is a defect in both genes in a pair of chromosomes. If there is a defect in only one of the genes, the disorder will not occur in that individual, but the person will be a carrier of the defective gene. This defective gene could then be passed on to that person's offspring, creating the possibility that it will lead to the disorder in later generations if a future partner is also a carrier. With autosomal dominant disorders, the disorder will occur if there is a defect in either of the genes. Only one gene has to be affected, so an individual with that single gene will exhibit the disorder; it is not possible to be a healthy carrier of a dominant disorder.

Heritable disorders can be monogenic (caused by an abnormality in a single gene), polygenic (caused by abnormalities in multiple genes) or multi-factorial (caused by a combination of abnormalities in multiple genes and environmental factors). Genetic abnormalities can also vary: a piece of the genetic code may be missing, it may be incorrect or there may be too much of it.

An example of a monogenic, recessive disorder is cystic fibrosis,¹⁴ a disorder that affects roughly 1,500 people in the Netherlands and which approximately 25 children are born with every year. This serious heritable disorder is caused by a single letter in the genetic code for the CFTR gene (cystic fibrosis transmembrane conductance regulator) being incorrect or missing.

That gene contains the instructions for the CFTR protein, which normally ensures that the mucus that body cells produce is thin and liquid. Because of the abnormality in this gene, the CFTR protein does not work properly and the mucus produced is far thicker and tougher than normal. This disrupts various physical functions in the lungs and the digestive system, for example.

A disorder that is caused because the genetic code of a gene is too long is Huntington's disease, a dominant disorder that is found in between seven and ten of every 100,000 Europeans.¹⁵ In people with Huntington's disease, the gene for the protein huntingtine is longer than it is in a healthy person because a piece of that code (CAG) is repeated too often at the end. The defective huntingtine protein causes a breakdown of neuronal cells, among other things. Healthy people have between six and 36 CAG repetitions, while persons with Huntington's disease have more than 40.

What is needed to repair an abnormality in a gene depends on whether it is due to a genetic code that is missing, incorrect or present in excess. If there is an excess of a genetic code, the relevant piece has to be cut away. However, to repair missing or incorrect codes, in addition to cutting the DNA in the right place, the missing, correct piece of DNA has to be inserted at that location. Research with mice, among others, has shown that DNA modification whereby a piece has to be inserted is considerably less accurate, effective and efficient than a modification in which a defective gene only has to be cut out.

Laboratory research with cells is currently being conducted into the modification of the genetic predisposition to monogenic diseases. It is hoped that this genetic predisposition can ultimately be modified accurately and safely in an embryo so that the child can be born healthy and the defective gene will no longer be passed on to their offspring.

Many disorders, traits or characteristics are caused by a complex and often unknown combination of multiple genes and environmental factors: these are known as multifactorial disorders. Most psychological disorders, cardiovascular diseases and cancers are multifactorial. Many genes also

14 <https://erfelijkheid.nl/ziektes/cystic-fibrosis>

15 <https://erfelijkheid.nl/ziektes/ziekte-of-huntington>

play a role in the formation of various disorders, traits or characteristics. It is, therefore, difficult to predict what consequences the modification of heritable DNA in an embryo will have for the physical functioning of that person and his or her future offspring. Even if a gene is modified correctly, there could be unforeseen (and negative) consequences for these future persons. A lot of research is still needed in this field. Because of the complex origins of such multifactorial disorders, only some of which are genetic, they cannot be altered with genome editing alone. In theory, however, the chance of having them could be reduced by modifying some or all of the genes that are known to play a role in the development of the disorder.

Different types of human genome-editing technologies are required to repair specific types of genetic defects. The accuracy, effectiveness and efficiency of each type of modification can vary greatly, which has an impact on the suitability of genome-editing technologies for preventing or reducing the risk of specific genetic complaints (see, for example, COGEM & Health Council, 2017 or Nuffield Council on Bioethics, 2016). This is relevant for the dialogue because the modification of heritable DNA in embryos is not a solution for *all* heritable diseases. For disorders where it is not, further research into alternative treatments is needed.

The debate on genome-editing technology is fuelled by developments in the technology and the current state-of-the-art, but it also transcends those aspects: the issue is not the technology *itself*, but whether its use can be acceptable and desirable. Under what conditions are we willing to permit laboratory research (with cells or embryos), research with humans (which leads to children being born), and future applications?

Although CRISPR-Cas9 is more precise than previous genome-editing technologies, it has become clear in recent years that it is not perfect and that significant risks are related to its use. To investigate the risks and find solutions for them, scientists are trying to use CRISPR-Cas9, for example, to modify a particular gene *in vitro* in an animal embryo, in human cells or in a non-viable human embryo. They are investigating whether the genome-editing technology causes the desired change in the correct position in the DNA (*effectiveness* and *efficiency*) and whether this change then appears in all of the embryo's cells. It is also important to know whether unintended changes are made in addition to the intended DNA

modification (*accuracy*) (Cogem & Health Council of the Netherlands, 2017). Such unintended modifications, known as *off-target mutations*, are one of the major safety risks of genome-editing technology (Nuffield Council on Bioethics, 2016, p.44). It is plausible that promising new genome-editing technologies and methods will be developed in the near future. But those new and better ways of editing DNA will also require research.

Gene therapy

When genome editing is used as a medical treatment, it is known as gene therapy. In that context, a distinction is made between *somatic gene therapy* and *germline gene therapy*, depending on the cells in which the DNA is modified. In this report, we refer to germline gene therapy as ‘germline genome editing:’ the alteration of DNA in reproductive cells or cells that could grow into reproductive cells. That is the heritable DNA that is passed on to future generations. With somatic gene therapy, the ‘normal’ cells in a person’s body are modified, for example in the lung or the liver. The therapy could, in theory, be used as a treatment for cystic fibrosis (see box), since if the defective gene in a lung cell is repaired in the lab, the cell could then again function normally (and, therefore, produce normal mucus). A problem with its application in practice, however, is that the human body consists of billions of cells. In other words, for the successful treatment of cystic fibrosis with somatic gene therapy, an enormous number of lung cells in the person’s body would have to be genetically modified.

The distinction between the use of genome editing technologies in reproductive cells or early embryos – from which future persons will grow – or in other cells of existing persons is, therefore, important for the dialogue. With somatic gene therapy, only cells in a person’s body whose function has been disrupted by the genetic disease are modified. The DNA in reproductive cells or cells that can grow into reproductive cells is not modified. The genetic modifications will, therefore, not be passed on to any offspring. With germline genome editing, they are. For example, if the genetic modifications are made to reproductive cells, a recently fertilised egg cell or a several-days-old embryo (that consists only of a few cells), the genetic modifications will be present in all of the cells of the person that grows from that embryo. The modifications will therefore also be present in his or her sperm or eggs and the modifications will be passed onto his or her offspring (and all future progeny). This possibility of modifications being passed on to future generations is another reason why germline genome editing is regarded as controversial and has been a subject of ethical reflection and discussion for decades. The national dialogue commencing on 9 October 2019 is concerned with the latter.

1.3 Discussions about new technologies at different levels

Ethical or public discussions about new and emerging technologies are always complex. The debate about the implications of modifying heritable DNA in humans is no exception. Discussions about emerging technologies can be conducted at different levels (following Allenby & Sarewitz, 2011):

- the direct consequences of a single technology (instrumental level);
- how a technology fits into the social context and how existing social and cultural structures will be affected;
- the embedding of the technology in the international context, and the ensuing worldwide consequences.

At the first level, the debate on human genome editing centres on the immediate consequences in relation to such issues as the clinical benefits and risks, informed consent, reproductive autonomy and personal choice regarding reproduction for prospective parents. The scientific (un)certainty surrounding issues such as safety and effectiveness and the freedom and responsibilities of those directly involved is an important topic in this discussion.

At the second level, the debate concerns the embedding of the technology in society and covers not only the practical consequences of a technology's application in practice but also the broader social implications. This encompasses issues such as how the possibility of modifying the DNA of future persons relates to public values such as equality or solidarity, how the technology fits in with existing legislation and regulations, the system of governance for the use of the technology, and how genome editing of embryos will influence the practice and perceptions of pregnancy and reproduction.

At the third level, the discussion relates to the global context and consequences. After all, the development, and possible application, of genome-editing technologies to modify the DNA of future persons occurs in an international context. These genetic modifications could also transcend generational and national boundaries and can, therefore, have global consequences. The human genome is also seen as something that is closely linked to the identity, and uniqueness, of the human species.¹⁶

With genome editing, there is also the *time dimension*: in addition to altering the DNA of a child before its birth, the DNA of all future progeny of that child is often altered. Future generations could suffer unforeseen, negative effects from intended

16 UNESCO describes the human genome as 'the heritage of humanity'.

or unintended changes in DNA. The dialogue is, therefore, not just about the here and now, but about future generations and future societies.

Another issue that is raised in discussions about new and emerging technologies is the public attitude towards science and technology in general. Opinions that do not relate so much to the application of a specific technology (in this case genome-editing technologies to modify reproductive DNA), but which help to shape views on its use and its social consequences. This extends to aspects such as people's views on whether technological development can be managed, whether or not a new technology will benefit society, and whether technology should adapt to existing standards and values in society or vice versa (Swierstra, 2009).

In chapters 2 and 3 we show that considering the three levels at which germline genome editing can have consequences (direct, societal and global), as well as the time dimension, helps to systematically determine what topics must be covered in a dialogue and how best to incorporate them.

1.4 History of national and international laws and regulations on germline genome editing

As mentioned above, the debate about human genome editing was being conducted well before the discovery of the CRISPR-Cas9 system. The possibility of modifying heritable human DNA and so designing the human genome had been anticipated in ethical discussions and the public imagination decades earlier. From a historical perspective, the genetic improvement of humans or the human species has been a delicate subject. The Nazis' research into eugenics is often mentioned in this context.¹⁷ On the basis of their ideas about genetically improving the human race, the Nazis sought to influence the genetic composition of the population by preventing specific ethnic groups, who were in their view inferior, from procreating. At the same time, it is questionable how relevant the concerns about such atrocities and malpractices are in a contemporary context, since they were imposed by an authoritarian regime. It is argued, for example, that such eugenic objections to genetic modification or improvement do not apply, provided it remains the individual's free choice.¹⁸ Nevertheless, it is useful to be aware of sensitive topics like this in the course of a dialogue.

¹⁷ Eugenics is research aimed at improving the genetic composition of a population.

¹⁸ The term '*liberal eugenics*' is used in that context.

Prohibitions and treaties

The debate about human genome editing has resulted in various national and international laws and regulations, which highlight the worldwide consensus that targeted modification of the genetic traits of future persons with genome-editing technologies is ethically unacceptable, at least for the time being.

In most countries, including the Netherlands and the rest of the European Union, human genome editing is prohibited by law (Ledford, 2015). In the Netherlands, the prohibition is laid down in the Embryo Act, which was adopted in 2002 when Els Borst was Minister of Health. The law prohibits the creation of a pregnancy with reproductive cells or embryos whose DNA has been changed (Embryo Act, art. 24 (g)) and the creation of human embryos specifically for research (Embryo Act, art. 24 (a)). The ban on creating embryos also prevents research intended to determine and improve the safety and effectiveness of modifying DNA in an early-stage embryo with genome-editing technologies such as CRISPR-Cas9. Research with human embryos is now only possible with embryos that are left over in the laboratory of a hospital or a clinic after an IVF treatment.¹⁹ These 'residual embryos' are already several days old and consist of hundreds of cells and are, therefore, not useful for research into early-stage genome editing in human embryos (Health Council of the Netherlands and COGEM, 2017). In other words, current legislation prohibits the alteration of the heritable DNA of future persons and research into technologies with which those alterations could be made in human embryos, or effectively makes them impossible. This type of research can be carried out with animal embryos, but because of the differences between them and human embryos, the research only provides limited insight into the safety and effectiveness of their application in humans.

The European Clinical Trial Regulation (2014), which enters into force in 2019, also prohibits the alteration of heritable DNA by providing that "No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity." (European Clinical Trial Regulation 2014, p. 51)

In addition to these prohibitions, various human rights treaties curtail modifications of the human germline. For example, the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) provides that the human genome is symbolic of the 'heritage of humanity'. According to Article 13 of the Council of Europe's Convention on Human Rights and Biomedicine, an intervention to modify the human genome may only be undertaken for preventive, diagnostic or

¹⁹ Multiple embryos are usually created for IVF treatments. The quality of the embryos is assessed visually and the 'best' is transferred to the womb. Other embryos can be frozen for a later attempt. Prospective parents can also donate the embryos to another couple or for scientific research, or can choose to have them destroyed.

therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants (Council of Europe, 1997).

Speaking in the House of Representatives in 2016, the Dutch Minister of Health Edith Schippers called for regulation rather than prohibition of germline genome editing (Kamerstukken II, 2016/17, 29323, 110). A year later the Health Council of the Netherlands also recommended lifting the ban on creating embryos specifically for research. That would allow laboratory research into genome-editing technologies applied to human embryos and, hence, possibly also the future use of those technologies to modify the DNA of future persons (COGEM and Health Council of the Netherlands, 2017). The Minister proposed three amendments to the Embryo Act,²⁰ including lifting the ban on the creation of embryos specifically for research (into the modification of DNA in the germline, for example). However, the Council of State advised against sending the proposal to the House of Representatives. The principal reason it gave was that the explanatory memorandum accompanying the proposal failed to adequately discuss the 'points of departure, interests and considerations that, having regard to the interest of protecting the embryo, underpinned the choices made' (Council of State, 2019, p. 3).

During the negotiations on the formation of the cabinet in 2017, the coalition parties (VVD, D66, CDA and ChristenUnie) agreed that there should first be a public dialogue before any amendments were made to the Embryo Act (Rijksoverheid, 2017). On June 4th 2018, the current government organised a roundtable meeting with the House of Representatives, at which the discussion focused on permitting the creation of embryos for the specific purpose of improving IVF technologies. The subject of germline genome editing was avoided during that discussion, but the rapid developments and widening debate on genome-editing technologies are now increasing the urgency of reviewing the existing legislation.

It is, therefore, the ideal time to start a national dialogue in the Netherlands, in which public opinion can be formed with the help of relevant information and with room for discussion of different considerations at different levels. The dialogue and the findings from it will then provide input for the political decision-making on the genetic modification of future persons. The question of whether or not to permit the creation of embryos specifically for research is also being discussed.

20 1. Permitting, under strict conditions, the creation of embryos specifically for scientific research into fertility, artificial reproductive technologies and heritable or congenital disorders.
2. Prohibiting a cytoplasmic hybrid (cybrid) created by implanting a human egg cell nucleus in an enucleated animal egg cell or a cybrid created by implanting an animal egg cell nucleus in an enucleated human egg cell from being allowed to develop for longer than fourteen days or being implanted in a human or in an animal.
3. Permitting gender selection if the child will be a carrier of a serious gender-bound heritable disorder (and not to prevent the disorder from occurring in the child itself).

At the international level, there is also reflection on and discussion of human genome editing, and there have been various calls in recent years to:

- draft international rules on research into germline genome editing in humans and the clinical application and regulation of such research (the establishment of the *World Health Organization advisory committee on Developing global standards for governance and oversight of Human Genome editing* in 2018 was an attempt to respond to those calls);²¹
- shape international reflection and dialogue (for example, during the two ‘Global summits on genome editing’ in 2015 and 2018 (Olson (ed.), 2016; NASEM, 2019), or the idea of establishing a ‘Global Observatory for Gene Editing’ (Jasanoff & Hurlbut, 2018));
- consider a temporary worldwide ban on the reproductive application of germline genome editing until adequate reflection has taken place at the national and international levels (see, among others, Lander et al., 2019).

1.5 The importance of a broad discussion

Consideration of social values

Various authors of scientific articles or opinion pieces have pointed out that the debate about the targeted modification of the genetic traits of future persons and how society should approach it is conducted mainly by biomedical experts; as is the case with other emerging biotechnologies (see, among others, Van Beers, 2019 and Jasanoff et al., 2015). As a result, the discussion is confined to techno-scientific issues such as clinical risks and benefits (the first level, see section 1.3). The risk is that reflection on the consequences for social relationships, societal relations or public values (level 2) could be pushed into the background. According to Jasanoff and her colleagues (2015, p.25), radical technologies such as CRISPR-Cas9 not only offer possibilities to “improve lives but shape our expectations, and eventually our experiences, of how lives ought to be lived.” In short, the debate about germline genome editing (both the technology itself and its application for modifying heritable DNA) is also concerned with how we wish to shape the future of our society. Such reflection calls for input from others besides scientific and medical experts – the participation and input of various individuals, groups and perspectives is required.

21 www.who.int/ethics/topics/human-genome-editing/committee-members/and.

1.6 Summary: points of departure for a public dialogue

By facilitating public dialogues on the subject of human genome editing and the creation of embryos specifically for research purposes, Minister Hugo de Jonge is implementing the terms of the coalition agreement. By doing so, he is creating room for members of the public to form an opinion and to participate in the decision-making process on a subject in which scientific, medical, social and ethical issues are closely entwined.

One of the challenges in designing a public dialogue is how we can usefully conduct a national debate on the desirability of targeted modification of the DNA of future persons with the help of genome-editing technology. In this first chapter, we have shown that the discussion is being conducted at various levels: the technical and scientific, the societal and the global. The time dimension also has to be considered: these issues affect us not only in the here and now, but also concern future generations and future societies. At the same time, the dialogue takes place against a background of a variety of contexts: historical, political, ethical, societal and international. General public attitudes towards science and technology also influence how people think about human genome editing. The issue also raises other questions on topics such as the creation of embryos specifically for research and issues concerning related biomedical technologies that increase the possibility of measuring, analysing and perfecting a human life. The targeted modification of heritable DNA is a further step in that respect, which raises new ethical and social issues because modifications are passed onto every future generation.

The starting point for the public dialogue is that at every level there must be room for a variety of perspectives, considerations and expertise which reflect the diversity in the Netherlands. This means that a wide variety of groups and stakeholders must be involved in it. More importantly, the participants in the dialogue must not only adopt positions in opposition to one another, but must also discuss the underlying values and considerations with each other so that they can form an opinion in a dialogue with each other. In the coming chapters, we will explain how we feel this can best be done – i.e., how there can be a fruitful dialogue in the Netherlands that serves as a model for and is connected with the international discussion and which can provide input for a regulatory system in which the care for and protection of current and future generations is central.

2 The discussion so far

With the emergence of CRISPR-Cas9, the rhetoric of the simplicity, precision and safety of the technology, combined with the promise that serious heritable disorders can be prevented, or even eradicated, has reanimated the discussion on the ethics and the regulation of the modification of the DNA of future persons. Because this experimental technology could, for the first time, make it possible to eliminate the genetic predisposition to certain hereditary diseases in an embryo and thus allow a child to be born healthy.

Approach

In this chapter, we examine the background of the laws and regulations governing this topic. What are the reasons for the prohibitions and other provisions concerning the modification of heritable genetic properties? We further analyse the debate about germline genome editing (both the technology that enables the modification of heritable DNA in human embryos and its possible applications) that has been conducted in Dutch newspapers in the last few years. We also describe the results of research into public opinion regarding germline genome editing, in the Netherlands and elsewhere.

2.1 The reasoning behind laws and regulations

As discussed in chapter 1, current legislation does not permit changes to be made to the heritable DNA of humans. Research into methods by which such changes could be made has been conducted on animals, human cells and so-called residual embryos, but human embryos may not be created for that purpose. This section describes the values and considerations that lie behind these national and international prohibitions.

2.1.1 National regulation

According to the explanatory memorandum to the Embryo Act, the ban on the clinical application of germline genome editing is based on both pragmatic (safety and effectiveness) and ethical considerations (Kamerstukken II, 2000/2001, 27 423, no. 3, pp. 45-46). For example, the legislation states that the technologies with which DNA could be modified were not yet sufficiently advanced to make targeted changes in the human genome at that time. Simultaneously, the legislature

anticipated that it would be possible in the future and stressed that it would then raise ethical issues, at the level of both the individual and the entire human species. For instance, there is the question of whether targeted intervention in the human genome offends, or is, in fact, respectful of an individual's dignity. Or the question of what the consequences would be for the natural diversity and evolution of humanity, and how much risk could be taken in that regard. Before the targeted modification of heritable DNA could be permitted, further reflection was needed on those issues, according to the explanatory memorandum.²² The legislature did not exclude the possibility of it becoming ethically acceptable (or desirable) in the future, in some circumstances, provided there had been ethical reflection – and sufficient progress had been made in genome-editing technology and its safe and effective application. For that reason, the legislature opted for a temporary prohibition, which can be lifted by royal decree.²³

A similar combination of pragmatic and ethical considerations also underlies the ban on the creation of embryos specifically for research. For the legislature, the basic principle for assessing scientific research with embryos was the principle of respect for human life. The explanatory memorandum stated that research with residual embryos (which remain after IVF treatment) and research with specially created embryos both infringe on that principle, but to differing extents. Research with residual embryos is permitted in the Embryo Act because the loss of those embryos is justified by the fact that life is created with (many) IVF treatments.

However, the creation of human embryos specifically for scientific research constitutes a more serious breach of the principle of respect for human life because the purpose of those embryos is not to create a new life. In that case, embryos are created, with the help of the donors of semen and egg cells, with the sole purpose of increasing scientific knowledge. The explanatory memorandum stated that such a breach can only be justified if the scientific research serves important values.²⁴ In addition to respect for human life and medical utility, international and public opinion must also be considered, according to the explanatory memorandum.

At the time the Embryo Act was adopted, there was little support for the creation of embryos specifically for research in the Netherlands. The practice was also almost universally prohibited. The Embryo Act, therefore, included the ban on creating embryos specifically for research – at least temporarily.

22 The explanatory memorandum stressed that these fundamental questions had to be answered before genome-editing technologies that enable the clinical application of germline genome editing had been developed.

23 In other words, the ban can be lifted without the need for both houses of parliament to pass a legislative amendment.

24 The explanatory memorandum gives the example of research into the improvement of IVF treatments.

2.1.2 International regulation and treaties

The prohibitions in international legislation are based on the belief that modification of the heritable genome of future persons affects individual and collective values, rights and interests. According to the explanatory report (Council of Europe, 1997b) accompanying the Council of Europe's Convention on Human Rights and Biomedicine (Council of Europe, 1997a), the ban on modifying the genome of future persons is intended to prevent eugenic practices. According to the report, the 'ultimate fear' is of intentionally modifying the human genome to produce individuals or entire groups endowed with particular traits (Article 13).²⁵ The fear is that with specific interventions in the human genome, human *reproduction* will be transformed into the *production* of humans.

According to UNESCO's Declaration on the Human Genome and Human Rights (1997), the human genome underlies 'the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity'.²⁶ The declaration states that the human genome should, therefore, be seen in a symbolic sense as the 'heritage of humanity'. UNESCO's bio-ethical committee, therefore, advocated then (and again in 2015) a provisional ban on interventions in the human germline, and called for 'reflection on all possible consequences for human rights and fundamental freedoms and the future of humanity itself' (IBC, 2015).

2.1.3 Summary: a mix of pragmatic and fundamental considerations

Accordingly, the Dutch and European restrictions and prohibitions relating to research with human embryos and germline genome editing are based on a mix of pragmatic and ethical considerations. The most important pragmatic consideration is that the safe and effective modification of the DNA of future persons is not yet possible with the current state of genome-editing technology. But as the explanatory reports show, the legislation and the regulations are not only based on pragmatic factors, but also on various ethical considerations, which, in fact, anticipate that at some point the technology will be available to allow for safe and effective germline genome editing. That possibility has drawn attention to the ethical

25 'The progress of science, in particular in knowledge of the human genome and its application, has raised very positive perspectives, but also questions and even great fears. Whilst developments in this field may lead to great benefit for humanity, misuse of these developments may endanger not only the individual but the species itself. The ultimate fear is of intentional modification of the human genome so as to produce individuals or entire groups endowed with particular characteristics and required qualities' (Article 13).

26 'The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity.'

aspects, because targeted modification of the human genome raises questions about the rights, liberty, dignity and identity of individuals, society and the entire human species. And creating embryos specifically for research raises questions about respect for, and instrumentalisation of, human life.

From a pragmatic to an ethical discussion

With the development of new genome-editing technologies like CRISPR-Cas9, it seems likely that technologies for safely and effectively modifying the human genome will soon be available. Consequently, the weight of the pragmatic arguments in favour of the current prohibitions will steadily decline. This has prompted a number of organisations in the Netherlands, including the Royal Netherlands Academy of Arts and Sciences (KNAW) (2016) and the Health Council of the Netherlands (2017), to recommend eventually revising the Dutch legislation. In the short term, that would involve lifting the ban on creating embryos for the purpose of scientific research, which would allow laboratory research into the modification of heritable human DNA and the technologies to facilitate it. These parties also advocate, in line with the government, that there should be a public dialogue on the ethical questions raised by this issue. They further argue that the absolute ban on the modification of embryonic DNA should be lifted if the public dialogue shows that there is sufficient public support in the Netherlands and if laboratory research shows that genome editing can be performed with sufficient safety and effectiveness. In that case, some applications, such as preventing certain serious heritable disorders, should be permitted under strict conditions. In light of the reasoning expressed in the explanatory reports to national and international regulations, the public dialogue should not only concern the safety, effectiveness and risks of existing technologies. Questions regarding the rights, liberty, dignity and identity of individuals, society and the entire human species should also be discussed.

2.2 The (public) debate about germline genome editing

Method

For our analysis of the debate currently being conducted in the public domain, we searched the digital newspaper database NexisLexis (www.lexisnexis.nl) with the keywords 'kiembaan(gen)modificatie'²⁷ (32 recent articles) and 'CRISPR' in combination with 'embryo' (159 articles). A selection was made from the results from the period between 2015 and February 2019 and from a collection of newspapers (*Financieele Dagblad*, *Trouw*, *NRC/NRC.next*, *de Volkskrant*, *Reformatorisch Dagblad*, *Nederlands Dagblad*). An effort was made to select a

²⁷ "germline (gene) modification"

variety of background articles, news reports and opinion pieces. We also conducted a search in the online archives of the *Groene Amsterdammer*, *Elsevier*, *De Correspondent* and *Vrij Nederland* with the same keywords:

‘kiembaan(gen)modificatie’ and ‘CRISPR’ in combination with ‘embryo’. Starting on January 1st 2019, we monitored the same newspapers, magazines and online sources for relevant publications on the subject, using the same keywords and related terms such as ‘cutting and pasting in DNA’ and ‘designer babies’. In reviewing these articles, we looked for the perspectives that were expressed, the arguments that were used to support this, the principles that were cited and any related themes that were mentioned.²⁸ In addition to newspaper articles, we also searched for other sources, such as reports of public meetings on the subject and documentaries on Dutch television.

It became clear from the newspaper articles that there is interest in germline genome editing and that discussions of the subject regularly resurface. The debate in the newspapers centred mainly on the medical benefits and the risks, but also addressed the wider consequences for individuals, society, and humanity as a whole. It became clear that views differ on when targeted modification of heritable human DNA is acceptable and what considerations play a role in forming an opinion. In the following section, we discuss a number of topics that, in our opinion, clearly emerged from the newspaper articles and other sources that were consulted.

2.2.1 Utility and necessity of germline genome editing

The potential medical benefits and the risks of modifying heritable DNA were frequently mentioned in the articles that were consulted. Many authors referred to potential benefits of modifying heritable DNA for prospective parents and their future children. In that context, it was often mentioned that it could prevent a lot of suffering caused by diseases, and that it might even lead in the future to the ‘eradication of terrible heritable diseases such as cystic fibrosis or Huntington’s’²⁹ (Keulemans, 2015). It was also mentioned that it would give parents with a heritable disorder, or who are carriers of it, the option of not passing the disorder on to their descendants. According to many authors, the fact that genome editing of embryos could be used for medical interventions to prevent illness and suffering supports calls for further research into its potential, and eventually to its application in practice.

²⁸ See the list of newspaper articles that were consulted.

²⁹ ‘uitbannen van afschuwelijke aangeboren ziekten als taaislijmziekte of Huntington’

It was also evident from the newspaper articles that many authors have serious reservations and doubts about the likelihood of it ever actually being possible to modify genes in an embryo in such a way as to prevent a heritable disorder from being passed on. They also question whether it could be done without having unintended harmful effects, referring to the scientific problems that still exist in relation to the technology, such as the complexity of the relationship between genes and the characteristics and traits for which they code. Disorders and desired traits are often influenced by many different genes, in combination with environmental factors. Furthermore, a single gene often performs multiple roles. Modifying those genes will then have an impact on different properties, characteristics or processes. This complexity makes it difficult to identify the right combination of genes to produce the desired results. At the same time, it is difficult to predict the ultimate effect of genetic modification, which applies to both the intended modifications and unintended, off-target mutations (see chapter 1).

Authors who call for permitting technologies for genetic modification of embryos (or research into it) generally also acknowledge the complexity and the risks. For them, however, that is no reason to ban them entirely. After all, they argue, the risks of such frontier science are always uncertain (see, for example, Bredenoord in De Rek, 2016). However, they do recognise them as a reason for proceeding with caution and for formulating conditions on the following aspects:

- *When* the technology can be applied responsibly: only after extensive preliminary research has shown that it is sufficiently safe and effective.
- *What* it can be used for: 'for the time being, only for gene mutations with a major influence on the existence of serious diseases (De Wert, 2016).
- *How* it should be regulated.

A frequently-mentioned reservation to the use of genome-editing technologies in embryos to prevent genetic disorders is that there is already an alternative. Under the current legislation, prospective parents can opt for embryo selection to prevent particular pathogenic genes from being passed on to their descendants without the need for changes to the genome of the embryo itself (see box 2 on page 23). Many authors, therefore, argue that germline genome editing has only limited added value compared with existing possibilities (see, for example, Santen & Hes, 2019; see also Van Gils, 2019). It is seldom the case that embryo selection is impossible (because, for example, there are no 'healthy' embryos to choose from) and that modifying the genome is the only option for prospective parents to have their own healthy, genetically related child. However, one advantage that is mentioned is that modifying the genome will protect future children not only from having the disease, but also from being carriers of it. They will, therefore, also not face the risk of passing on the pathogenic gene to their offspring.

2.2.2 Wider consequences for individuals, society, and humanity

According to some authors, the possibility of modifying the genome of future persons and generations raises concerns and issues that cannot be addressed in terms of direct risks and benefits. They refer, for example, to the fact that if parents can make far-reaching decisions about their children's genes, human reproduction will be transformed into the *production of humans*, which could lead to the disappearance of the legal distinction between a person and an object (see, for example, Pesser, 2017, Van Beers, 2018a). This is an important distinction in legal and ethical thinking, and is based on the intrinsic value of the individual. The disappearance of that distinction could have major consequences. For example, if parents have a child with different traits than they 'ordered', would they be able to hold someone liable, just as companies are liable for the products that they supply? There are examples worldwide of situations involving such 'wrongful birth' or 'wrongful life' cases (see Van Beers in Vaessen, 2017).

It has also been pointed out that the targeted modification of the human genome could have radical consequences for social relationships: first, in terms of the availability or affordability of the treatment. If it is only available to people who can afford it, socio-economic differences could be reflected in people's genes, and thereby be reinforced. In other articles, authors or interviewees have expressed the concern that this could deeply alter the relationship between parents and children.

It could also lead to stigmatisation of people with heritable disorders, undermine the right of children to an open future, or, in fact, impair the freedom of prospective parents if changing heritable traits of future children becomes the social norm (see, for example, Geesink, 2017; Mulder, 2018; Keulemans, 2015 and Boon, 2016).

Some authors have pointed to the fact that human DNA is not simply biological material, but also has value because it is closely linked to our identity as individuals and as humans (which is an important principle behind UNESCO's Declaration on the Human Genome and Human Rights, see also Van Beers in Vaessen, 2017; Herzberger, 2018). However, the relationship between the human genome and identity is a controversial subject. It is felt by some that a term like 'genetic identity' wrongly assumes that human identity lies entirely in the DNA. They argue that an individual's identity is only partially influenced by fixed genetic properties, and is, in fact, constructed by people themselves – and is, therefore, more dynamic (see, for example, Smalbrugge in Van Houten, 2019). From the perspective of a dynamic concept of the term, identity depends heavily on factors such as a person's self-image or social context and making modifications in the DNA does not automatically affect a person's identity.

In articles about the consequences for the individual, society, and humanity that have been written from a Christian perspective. For some authors, the dignity of human life is connected to the Christian belief that 'all people are children of the same Divine Father' (Seldenrijk, 2019)³⁰. To them, our DNA is the only thing that everyone has in common and must, therefore, be protected against modification. For others, the possibility of preventing diseases, and hence suffering, is in line with Christian belief because Jesus Christ also engaged in healing (Smalbrugge in Van Houten, 2019).

2.2.3 Similarities with earlier discussions

In other words, various arguments, concerns and considerations are put forward in the discussion about the targeted modification of heritable DNA. Some relate to its utility and necessity and focus on the specific technology and its direct consequences. Others address the broad consequences for the individual, society and humanity and focus on ethical principles or values, such as dignity and solidarity.

The authors differ in their views on the relevance and importance of the various arguments and the weight that should be assigned to them. The discussion about the desirability of using genome-editing technologies to modify the human genome must, therefore, also address the question, which is often implicit, of whether they raise new ethical questions. Proponents of allowing these technologies (and research into them) often refer to similarities between those technologies and the following:

- existing medical interventions, such as embryo selection, where it is possible to choose an embryo with a specific genetic profile;
- natural processes, such as the spontaneous occurrence of mutations in the germline; or
- historical developments, such as the fact that reproductive technologies always initially raise moral objections but later become widely accepted (IVF, for example).

With these comparisons, they argue that, although the *technological possibilities* of making targeted genetic modifications are new and revolutionary, from a moral perspective the envisaged *applications* are not new. They only increase the possibility of achieving accepted goals, such as preventing heritable disorders from being passed on to descendants. In other words, they contradict the arguments and considerations presented at the beginning of this section, where it was asserted

³⁰ "alle mensen zijn kinderen van dezelfde Goddelijke Vader"

that modifying the genome of future children, and the technology that allows it, does raise new ethical issues. The articles studied reveal that there is still considerable disagreement about what precisely is at stake.

2.2.4 Distinctions between desirable and undesirable applications

There seems to be a broad consensus on the question of what DNA modifications of offspring should or should not be allowed. Practically every author rejects the use of germline genome editing to make genetic enhancements – to influence intelligence or the colour of the eyes, for example. But there is no general agreement on what precisely that implies for the acceptability of genome editing. Many authors point to the difficulty of making a distinction between medical applications and applications intended for human enhancement (the distinction between ‘making people better’ and ‘making better people’) (Pessers, 2017 and Van Beers, 2018b). The term ‘disease’ is hard to define and depends on prevailing standards and values, which can also change over time. These authors, therefore, assert that strict regulation is illusory and warn of the danger of a slippery slope towards human enhancement.

Many authors who see the DNA modification of human embryos as a potentially valuable medical intervention are unimpressed by the ‘slippery slope’ argument. They assert that the pitfalls can be avoided with regulation and oversight and have confidence in the regulatory capacity of science and society (Repping in Engels, 2018; De Wert & Dondorp, 2016; Bredenoord in De Rek, 2016). They also often refer to the complexity of genetics in arguing that concerns about human enhancement and spectres such as the ‘designer baby’ are unrealistic (Boon, 2016; Van Gils, 2018).

2.2.5 The discussion about research with embryos

As described in chapter 1, scientists assert that embryos created specifically for research purposes will ultimately be needed to investigate the safety and effectiveness of human genome-editing technology. Consequently, the embryo discussion is closely entwined with the discussion about germline genome editing. In chapter 3, we discuss the ethical issues associated with embryo research in more depth. In this section, we look at the questions raised in newspapers in the public debate about embryo research.

In the newspaper articles that were consulted, some authors expressed hope, for example, that the use of genome-editing technologies to modify genes in embryos

might in the future lead to fewer human embryos being destroyed than with the current practice of embryo selection. In theory, only one embryo has to be created for the successful use of genome-editing technologies to modify heritable DNA. The desired genetic modification is then introduced into that embryo, leaving no residual embryos. On the other hand, more embryos might have to be created and destroyed during the pre-clinical phase of the research (Jochemsen in Boon, 2016).

These views also raise the question of whether it is possible to investigate the safety and effectiveness of technologies with which changes can be made in embryos without having to create and destroy them. A possible alternative might be to carry out extensive research on embryos of animals and primates or on synthetic embryos (human stem-cell structures that appear to possess certain characteristics of embryos), or to make genetic modifications in precursors of reproductive cells (Jochemsen in *Nederlands Dagblad*, 2017). Knowledge of such alternatives will, therefore, play a role in the public dialogue.

2.2.6 Complexity of the international context

In the newspaper articles that were studied, there were frequent references to the fact that it is difficult, if not impossible, to prevent the development and application of technologies such as genome editing (see, for example, Repping in Koelewijn & Weeda, 2019). In some articles, this idea is expressed explicitly with a phrase such as 'The genetic babies are certain to come' (Keulemans, 2018, Mastenbroek and Repping, 2018). But many authors also refer to the competitive international context in which modern biotechnology is developing and the difficulty of regulating a global market in such technologies (see, for example, De Wert & Dondorp, 2018). They regularly mention the risk of 'medical tourism'. Even if the law in the Netherlands continues to prohibit modification of the genome of future children, couples will be able to travel to a country where it is permitted.

It is worth noting that this observation does not generally imply moral resignation, but is framed in terms of an appeal for timely political and public reflection on the new technological possibilities to modify genes and offspring and the conditions under which they can be used responsibly in the Netherlands (see, for example, De Wert & Dondorp, 2018; Santen & Hes, 2019; Cornel, Smalbrugge & Haselberg, 2019).

In that context, some authors refer to the Netherlands' exceptional position in the field of reproductive medicine. In the Netherlands, fertility treatments fall under the regular health-care system. In some countries, such as the United States and Spain, couples who wish to use IVF and other fertility treatments can also go to

private clinics. This has created a vibrant 'IVF industry' in those countries, where clinics offer a variety of treatments that have not been proved effective, with the promise that they will increase the chance of having a baby (Stelling, 2018). Couples in the Netherlands who want a child can also go to a private clinic in another country. For some authors, this is a further reason to permit and encourage research in the Netherlands. In the first place because it would generate independent and high-quality information about the safety and effectiveness of the treatments that are offered in other countries, and Dutch health-care professionals would, therefore, be able to provide their patients with better information about the risks and the clinical effectiveness of those treatments. In the second place, because Dutch scientists and health-care professionals could join international professional groups and participate in discussions of the practices in other countries.

2.2.7 Summary: little agreement in the public debate

In short: the development of new genome-editing technologies such as CRISPR-Cas9 has re-opened discussions in the newspapers about the acceptability and desirability of germline genome editing. We observe two approaches: in the first, the direct consequences (the 'utility and necessity') of the technologies are central, and modification of the DNA of future persons is seen as a potentially valuable medical intervention for preventing serious heritable diseases. From that perspective, it is of primary importance to guarantee the safety and effectiveness of the technologies and to properly regulate their application. Proponents of this approach often advocate allowing laboratory research with human embryos created specifically for the purpose to establish and improve the safety and effectiveness of genome-editing technologies.

In the other approach, the key aspect is the broader consequences of targeted modification of the human genome for the individual, society and humanity. Proponents of this approach mainly warn of the possibility of reproduction becoming the *production* of children and that targeted intervention in a person's genome can have unforeseen consequences, also in terms of dignity, integrity and identity, for future generations and in future societies.

Almost all authors agree on the need to conduct a public dialogue. However, there is disagreement on what precisely is at stake and, hence, what the subject matter of the dialogue should be.

- For some, it is mainly concerned with developing and introducing a safe and effective method of preventing the transmission of genetic disorders. They attach most importance to the medical benefits, the risks and regulation, and

less to the fundamental objections or the broader consequences for individuals, society and humanity. However, they do recognise the difficulty of determining, on the basis of biological criteria, what modifications are or are not desirable and to what extent the risks are acceptable. This would have to be determined in a broad dialogue (see, for example, Santen & Hes, 2019).

- For others, what is at stake are fundamental values and the broader consequences for future generations, which are impossible to foresee. They feel the first approach is often too limited: if the discussion is confined to practical issues and risks, they feel, fundamental issues will fade into the background when they should, in fact, be at the forefront of the dialogue (Van Bodegom & Vos, 2017; Geesink, 2017; Van Beers, 2018a&b).

The positions adopted on these issues influence, often implicitly, a person's views on what the subject of the dialogue should be and what arguments and voices should be authoritative in it. It is, therefore, also important for these implicit considerations to be reflected on in the dialogue on the modification of heritable DNA.

2.3 Public opinion research into the modification of heritable DNA

2.3.1 Public opinion research in the Netherlands

There have been several studies in recent years to survey public opinion in the Netherlands on the modification of the genetic properties of future generations. Two of these studies took the form of extensive public surveys of people's views on genetic modification. One of them combined a focus group (four groups of eight participants) with a survey of 1,031 respondents (COGEM, 2019b). The other study surveyed opinions on modern biotechnology via an online research platform on which 150 respondents posted more than 3,500 messages (Wouters & Rerimassie, 2017). These studies covered many subjects but contained several questions about the modification of the heritable DNA of humans. Two online surveys have also been conducted. In the first (Van Dijk & Luitwieler, 2019), the respondents were members of the Dutch Patients Association (NPV), a Christian organisation, the Lindeboom Institute and readers of the *Reformatisch Dagblad* newspaper (2,101 respondents, hereinafter referred as 'the Christian population') and the general Dutch population (a representative group of 512 respondents aged 18 and older). In the context of embryo research, they were asked about their familiarity with and opinions on human genome modification.

In early 2016, *De Kennis van Nu*, a public television programme devoted to science and technology, asked its audience (1,013 respondents) for their views on various forms of human genetic modification, from gene therapy in adults to the modification of the genetic trait of an embryo to make a child more intelligent (Van der Lente, 2016; Hendriks et al., 2016).

The results of these surveys of public attitudes showed that the respondents were often not fundamentally opposed to applications of germline genome editing. The main determining factor in whether they found it acceptable was the purpose of the modifications (COGEM, 2019b; Wouters & Rerimassie, 2017; Hendriks et al., 2016). More than half of the respondents were positive towards applications designed to prevent disease: 59% (Wouters & Rerimassie, 2017) or 66% (Hendriks et al., 2016). Roughly half of the general population felt that genetic modification of embryos to prevent serious heritable diseases was a good reason to conduct embryo research (Van Dijk & Luitwieler, 2019); among the Christian population, however, the figure was 10% (Van Dijk & Luitwieler, 2019).

The percentage of respondents that accepted the use of germline genome editing to reduce the chance of a disease (rather than preventing it) or to improve certain traits is considerably smaller (30% for HIV-resistance and 16% for high intelligence, Hendriks et al., 2016). Only 9% of the Dutch population felt that embryo research was justified to 'cultivate embryos with desired characteristics', and the figure among the Christian population was 2% (Van Dijk & Luitwieler, 2019).

In other words, for most participants, the distinction between healing and enhancing was relevant in assessing the acceptability of genome editing. The same applied for the distinction between preventing a disease and reducing the chance of having it. For the majority of respondents, applications for enhancement are a step too far, although there was evidence in the surveys that there are some who think otherwise. A major concern expressed in the public surveys was that this type of biotechnology would only be available to wealthy people. Fear of the unknown and the unpredictable was another factor in how participants judged such technologies (Wouters & Rerimassie, 2017). For biotechnology in general, commercial interests and scientific curiosity were seen as a threat to the responsible use of the technology (Wouters & Rerimassie, 2017; COGEM, 2019). The public surveys discussed here give a general impression of attitudes towards various applications of modifying the DNA of future persons. However, only limited conclusions can be drawn from them as regards public opinion in the Netherlands, because many of the surveys either were not primarily concerned with modification of human

heritable DNA or the samples were not representative.³¹ There have been more extensive public surveys in some other countries.

2.3.2 Public surveys in other countries

In Belgium, a survey was carried out in 2017 among 1,000 people in Flanders, with a representative distribution in terms of age and gender (De Cleene, 2017). According to the survey, 61% found the idea that genes can be altered scary, 68% felt that 'a person loses a piece of their unique identity when his/her genes are altered' and 51% feared that DNA modification could have unforeseen negative consequences. In Belgium, support for modifying heritable DNA to prevent serious diseases was also greater (86%) than for human enhancement by scientists (29%) or for the selection of traits in an embryo by parents (3%). Acceptance was greater if it was not mentioned that modifications would be passed on to offspring – 95% then agreed to changes in heritable traits to prevent diseases, 38% to enhancements in persons by scientists and 9% to allowing parents to select traits of an embryo. Whether heritable modifications will be passed on to future generations, therefore, seems to affect the degree of acceptance.

In the United Kingdom, an extensive survey of public opinion towards possible applications of genetic technology in humans, animals and plants was carried out in 2017 (Van Mil, Hopkins & Kinsella, 2017). The study combined a public dialogue with a survey (with a representative sample of 2,061 participants). The public dialogue involved two rounds of debate on applications of genetic technology in humans with a group of 26 to 29 participants. When asked to give their opinions on a case study in which genetic modifications were made to prevent a heritable disease, 76% of the respondents in the survey were positive, compared with 15% for applications to make enhancements. Objections expressed during the public dialogue were the risk of further segregation of society and the undesirability of a society in which everyone is perfect.

In the US, various surveys have been conducted on related themes in the last three decades. In a summary of the findings in 2016 (Blendon et al., 2016), it was shown that a minority approved of modifying the genetic traits of offspring if it would prevent serious heritable diseases (26%-46%). Acceptance was lower for modifications to influence intelligence, physical characteristics or appearance (8%-28%). Almost half (49%) of the Americans would consider modification of the genetic properties of their offspring if it would benefit their children's health. These results are similar to the outcome of a survey in Australia, where acceptance of

31 This means that the participants in the studies were not representative of Dutch society.

DNA modification in human embryos also depended on its purpose and was greater for applications that would improve the health of offspring than for applications to enhance a person's characteristics (Critchley, 2019).

It should be noted that the national and international studies discussed above consisted mainly of public surveys based on questionnaires that were completed by the participants, often in response to limited information or a case study. However, a visible pattern emerges from the surveys: modifying the genetic traits of offspring is controversial and its acceptance depends on the purpose of the application. Preventing serious heritable disorders is regarded as an acceptable application more often than human enhancement. However, this disguises the more nuanced considerations that emerged in focus groups, where participants discussed the issues and had more time to form an opinion. Those discussions covered considerations such as anticipated and unforeseen risks, the possible impact on society, the fair sharing of benefits and drawbacks, and the need to provide comprehensible information so that parents who want a child in the future can make an informed decision (see, for example, Van Mil, Hopkins & Kinsella, 2017). To arrive at an informed opinion, the general public needs to be engaged with the subject, have the direct and social consequences explained to them and take part in a public dialogue in which they can reflect on the arguments of others.

2.4 Conclusion: from a narrow discussion to a broad public dialogue

The views expressed in the debate in the Dutch newspapers are mainly those of experts, such as scientists, medical professionals, ethicists and lawyers, who put forward various arguments. Patients and representatives of patients sometimes also have a say. The views of the general public are partially represented in public surveys conducted in the Netherlands, but for the majority of those surveys, the participants were not able to engage in a discussion.

Although the insights from the newspaper articles and public surveys do help to give an impression of the relevant considerations, there has never been a *broad public dialogue* on this subject in the Netherlands: a process of collective opinion formation in which various perspectives and considerations are shared and members of the general public are involved and encouraged to form their own opinion.

The Rathenau Institute has years of experience in organising public dialogues on new and existing technologies that could have a major impact on individuals,

groups, practices, social structures and collective values.³² We know from these earlier dialogues that while focus groups and panel discussions give the public a voice on a small scale, the real purpose of a public dialogue is to inform a wider audience and engage them in the discussion of a complex subject. In that context, it is not only important to provide information about the technology and what it can be used for, but also to encourage people to think about and reflect together on the broader social consequences. Earlier public dialogues, such as the one on nanotechnology (Hanssen, Walhout & Van Est 2008), have taught us that where topics relating to complex technology are concerned, people must be able to inform themselves about the relevant social and ethical issues, such as potential consequences for the individual and society and for current and future generations. In the public dialogue about germline genome editing, the modification of the DNA of future persons and the technologies that enable it, there must be an opportunity for proper reflection on how this technology could alter society and social practices – and who will enjoy the benefits or suffer the disadvantages. Experts in medical science must, therefore, adopt a *different* role in the dialogue: they are not only *providers* of information, but also *participants*. Input of various perspectives and forms of expertise is also important.

An important building block for public dialogue is mapping the social and ethical issues that play or could play a role. In the next chapter, we provide a survey of issues that arise in connection with the modification of the genome of future persons. Together with techno-moral future scenarios (see part II of this report), they could help to stimulate thinking about the broader social consequences of germline genome editing.

32 See, for example, the dialogues on nanotechnology (Hanssen, Walhout & Van Est, 2008); synthetic biology (Rerimassie & Stemerding, 2012); nuclear waste (De Vries et al., 2015); the energy transition (Van Est, Waes & de Vries, 2016); geothermal energy (Smink 2017); and the combination of human and animal cell material (Van Baalen, Gouman & Verhoef, 2019).

3 Social and ethical issues of germline genome editing

In chapter 2, we described the considerations behind the legal instruments that prohibit the modification of heritable DNA in human embryos or reproductive cells, and provided an overview of the public debate that has been conducted on the subject, particularly in newspapers and magazines. We concluded that there has not yet been a broad public dialogue on whether it is acceptable to edit specific genes in persons and, if so, for what purposes. This chapter contains a systematic analysis of the ethical and social issues that need to be addressed in such a dialogue. On the basis of the literature and the information discussed in chapter 2, we found that opinions are divided on this issue. Some people feel that the targeted modification of a future person's genome is always fundamentally unacceptable, regardless of the specific purpose of research or the potential medical applications. For many others, the acceptability of human genome editing is closely linked to considerations such as the possible medical benefits or the consequences for society. During the discussion, many of these issues, and the various positions on them, remain implicit. They are background factors in the explicit arguments, objections and claims that people make. The review of social and ethical issues in this chapter might help to make these concerns explicit and so ensure that they can be discussed in the forthcoming dialogue.

Approach

To understand the ethical and social issues that are relevant for a dialogue on the acceptability of modifying heritable DNA in human embryos or reproductive cells, we have mainly consulted reports by national and international advisory councils and ethics committees dealing with the subject. We also conducted fourteen interviews with representatives of groups and parties that are engaged with or have an interest in public dialogue on the subject: scientists, health-care professionals, representatives of patients and other stakeholders.³³

In the interviews, we asked the respondents about three themes:

- Their views on genome-editing technologies for targeted modification of heritable DNA (germline genome editing). What expectations, concerns and hopes play a role? What are the relevant challenges and opportunities? What in their view should be the policy towards this technology?

33 See Appendix 1 for a list of interviewees.

- Their views on the dialogue. Who are important stakeholders in the dialogue? How can we reach them? What subjects could be discussed and what is the best way of discussing them?
- Expectations for the future of targeted germline genome editing. What, in their opinion, is a realistic future scenario for this technology? For whom should it be used in practice? And what do they believe the broader social consequences will be?

3.1 Questions in three domains

As explained in chapter 1, a discussion about complex issues (germline genome editing in this case) can be conducted at three levels: the *technology itself* (the instrumental level, for example its safety and applications); the *embedding of the technology* in society (where, in this case, not only the consequences for reproductive practice have to be considered, but also the wider social implications such as solidarity with those suffering from an illness); and, finally, the *global context* (for example, the differences in international legislation in terms of the scope for research into or application of the technology). By thinking about and discussing the issues at each of these levels, people can arrive at an informed opinion the modification of hereditary DNA in embryos.

However, the discussion cannot simply be conducted systematically at these levels. Because there are still great uncertainties about scientific, technological and international social developments, there is a lot of confusion about what precisely is being discussed, who is affected and who can take part in the discussion. Are we talking about a technology that will only be used in the lab, about the need to investigate a possible medical intervention, or about what we will use the technology for and what consequences it will have for the practice of reproduction and for society? Should we confine the discussion to the Netherlands, or also look beyond the national borders? To elucidate these questions, in this chapter we make a distinction between three domains in which ethical and social issues arise in relation to the targeted modification of heritable DNA in human embryos and reproductive cells:

1. The domain of research in the laboratory
2. The domain of research with humans
3. The domain of application in practice

Although these domains are interlinked, they do not represent successive steps or levels. However, dilemmas that might arise in the first one are the most topical, since scientists who wish to work on genome-editing technologies to modify the

DNA of embryos in the laboratory are already confronted by this discussion, while the dilemmas that arise in the third domain relate to future generations. The subject, therefore, affects us all. Our objective in dividing the discussion into three themes is to make it clear that different social and ethical issues connected with germline genome editing arise in each of the three domains. Simultaneously, we want to underline the fact that these issues are intertwined: the desirability or otherwise of pre-clinical research into genome-editing technologies in the laboratory depends, for example, on estimates of the opportunities, risks and social consequences of clinical applications. And the acceptability or otherwise of clinical research whereby humans are born with a modification to their heritable DNA depends, for example, on the results of pre-clinical research. In other words, *whether* and *for what purpose* gene modification is desirable are closely connected questions, which have to be addressed at each level.

3.2 Domain of research in the laboratory

In various laboratories around the world, scientists are researching genome-editing technologies with which heritable DNA can be modified. In addition to improving existing technologies or developing new ones, researchers are trying to determine how effective these technologies are in removing or repairing genes that cause fatal diseases. In the process, they are trying to establish the safety and effectiveness of these technologies. For the dialogue, the important thing is not so much how genome-editing technologies such as CRISPR-Cas9 work, but rather what research with and into these technologies actually involves. Relevant considerations include not only the possibilities and limitations of laboratory research for establishing the safety and effectiveness of germline genome editing, but also what is needed to carry out this research. In that context, whether or not to use human embryos (including residual embryos) in laboratory research is a particularly important question.

3.2.1 Considerations relating to the creation of embryos for research

The discussion about laboratory research into human germline genome editing is inseparably linked to the debate about research with embryos. A widely shared view among scientists is that research with human embryos that have been created specifically for that purpose is essential for adequate research into germline genome editing in the laboratory (see, for example, COGEM & Health Council of

the Netherlands, 2017). As explained in chapter 1, this type of research is currently prohibited by the Embryo Act. The acceptability of research into genome-editing technologies to modify the DNA of human embryos and reproductive cells also depends on the acceptability of creating embryos for research purposes. It is, therefore, important to involve views on that issue in the discussion.

Attitudes towards research with embryos will differ according to a person's opinions on a number of questions. The first is the moral status of embryonic life; the embryo should be protected because of that status, and restrictions and conditions should, therefore, be imposed on research for which embryos are used – and ultimately lost. A second topic is whether it is acceptable to create embryos specifically for research. This coincides in part with the issue of the protection of embryos; if the existing ban is lifted, more embryos will be created and destroyed. But it also raises the question of whether creating embryos for research could potentially go too far in reducing human life to a means to an end ('instrumentalisation'). These embryos would not be created to grow into humans (as is the case with residual embryos that remain after IVF treatment), but purely to serve as research material. The third question is whether such objections based on the protection and instrumentalisation of embryos justify a ban on research into germline genome editing in humans when weighed against its potential benefits. And if embryos are created for research purposes, more semen and egg cells will have to be donated. Donating egg cells is burdensome for women and is accompanied by health risks, which is another factor that has to be taken into account.

Interconnectedness of the two discussions

During the public dialogue, attention will, therefore, have to be devoted to the question of whether research into genome-editing technologies for modifying the DNA of human embryos and reproductive cells is justified if it means that embryos have to be created specifically for that research. Quite apart from the dialogue on the modification of heritable DNA in humans, it is, therefore, important to discuss the creation of human embryos for research, the range of opinions on the subject and the values and considerations that underlie those views. Parallel to the National Dialogue on Human Genome Editing, the Ministry of Health, Welfare and Sport has commissioned the consultancy and communications agency Schuttelaar & Partners to organise public dialogue on 'the creation of embryos specifically for research', with a view to various research purposes, such as gaining insights into early embryonic development or improving IVF treatments. This dialogue will be conducted from June 2019 until the end of May 2020 and could, therefore, further deepen the dialogue on germline genome editing. For discussions about germline genome editing, it is important to explain the relationship between the two subjects and which of the two dialogues is the appropriate forum for a discussion of specific issues, questions and considerations.

3.2.2 Safety and effectiveness of laboratory research

There is a broad worldwide consensus that genome-editing technologies must be sufficiently safe and effective before they may be used for clinical purposes – a minimum requirement that has not yet been met (see, for example, German Ethics Council, 2019; Brokowski, 2018).³⁴ As described in section 1.2, various groups of experts and advisory bodies in the Netherlands and other countries have, therefore, argued that more pre-clinical research is needed to establish and improve the safety and effectiveness of genome-editing technologies before any decision can be made to allow their use.

Research into the safety and effectiveness of modifying heritable human DNA in the laboratory, therefore, focuses on establishing and improving the properties of genome-editing technologies that are *known* to be essential for the safe and successful clinical application of germline genome editing. However, the long-term consequences and risks for persons whose genes are modified cannot be assessed in the laboratory, or predicted on the basis of tests. Human genetics are too complex for that: many properties and processes are managed by a large number of genes (and often by environmental factors as well) and many genes are involved in multiple processes.

This complexity makes it practically impossible to predict the effect of altering a particular gene. That can only be investigated by transferring embryos with modified DNA into a womb, allowing them to grow into babies, and then watching them grow into adults.

In other words, research in the laboratory can establish whether genome-editing technologies are *effective*, *efficient* and *accurate*, but cannot predict the precise effects that genetic modification of an embryo will ultimately have on the resulting adult. Accordingly, research conducted in the laboratory can only partially remove the uncertainty surrounding the effects and risks of targeted modification of the DNA of future persons. In the public dialogue, it will be important to clarify which aspects of safety and effectiveness can be investigated with laboratory research, and which cannot. This will also provide a clearer picture of what scientists mean when they say that the technology cannot yet be applied to embryos from which babies will grow because the technology is not yet 'proven safe and effective'. It will also demonstrate what uncertainties will remain when clinical research with humans is being considered.

34 NB: a sufficient degree of safety and effectiveness is a minimum condition for its ethically acceptable application. That does not mean that when this condition is met, its application is also morally acceptable.

3.2.3 Summary: the dialogue is about research in the laboratory

In the public debate, the discussion often quickly turns to the desirability or otherwise of the targeted modification of the DNA of future persons for specific purposes. In this section, we have shown that the acceptability of the technology is also connected with questions and uncertainties that arise in the domain of laboratory research. For the public dialogue, it is, therefore, important to make the following clear:

- what outstanding scientific and technological questions there are in connection with the use of genome-editing technologies to modify the DNA in human embryos and what is required to answer those questions;
- what research into these technologies and their application in the laboratory actually involves, and what possibilities, constraints and uncertainties there are in establishing their safety and effectiveness with laboratory research; and
- that laboratory research into genome-editing technologies to modify the DNA in human embryos is inseparably linked with the discussion about the creation of embryos for research.

3.3 Domain of research with humans

In section 3.2, we showed that the safety and effectiveness of targeted modification of the DNA of future persons can only be established to a limited extent in the laboratory. Long-term effects and risks can only be investigated by creating a pregnancy with embryos modified in the laboratory and by allowing a child to be born from them. This raises specific ethical issues and considerations.

3.3.1 Weighing uncertain risks against uncertain benefits

Research into genome-editing technologies to modify the DNA in human embryos or reproductive cells in the laboratory differs in many respects from clinical research into the genetic modification of future persons. At present, embryos used for research in the laboratory may not be more than 14 days old. They are also not used to create a pregnancy. The effects of modifying heritable human DNA can, therefore, only be investigated in a few cells, through the initial development of the embryo. In section 3.2, we showed that, as a result, the safety and effectiveness of these technologies can only be investigated to a limited extent.

To gain a more complete impression of a technology's safety and effectiveness, experiments in which children are born from an embryo whose DNA has been modified with genome-editing technology. These children could enjoy the envisaged beneficial effects, but also possibly suffer unintended negative effects. This raises the question of what scientists must have investigated and established in the laboratory before we feel that the technique can be safely tested in a clinical setting. Also relevant is how the potential risks of clinical research from which children are born weigh up against the possible benefits.³⁵ What *criteria* play a role in that regard? Who should have *the final say* on that? And how can we address the fact that the future person whose heritable DNA has been edited has no say in the matter? The parties concerned could, depending on their convictions and interests, have differing views as to whether the potential benefits outweigh the possible risks. Furthermore, in weighing the benefits and risks there will also be considerable uncertainty about the likelihood and scale of unintended negative effects.

For the public dialogue, it will, therefore, be important to make it clear that at some point a balanced decision has to be made. There will have to be a discussion of the degree of uncertainty that will be acceptable in making this decision, the relevant values, considerations and interests, and who will have the final say.

3.3.2 Considerations for precautionary measures

Research into germline genome editing differs from that into other medical interventions on persons because changes in DNA are permanent and irreversible and are passed on to future generations. The targeted modification of DNA in embryos from which children grow can, therefore, have unintended effects with major consequences, not only for the person whose DNA has been modified, but also for all of his or her descendants and the human species as a whole.³⁶

Various precautionary measures could be taken to reduce the risk of harmful, unintended effects from germline genome modification research with humans (see,

35 Various national and international advisory reports have formulated conditions that have to be met before this step can be taken. For example, the concerns about safety and uncertainty surrounding effectiveness must be *sufficiently* removed through basic and pre-clinical research (German Ethics Council 2019). In conducting clinical research during which children are born, the relationship between potential benefits and risks for the future children must be *reasonable* (NASEM, 2017). These conditions are not very precisely formulated and could be interpreted differently by different stakeholders. In the dialogue, it will be important to discuss *what* is sufficient in terms of removing concerns and uncertainty and *when* we will find that the balance between benefits and risks is reasonable.

36 Because germline genome editing has an impact on future generations, it can also have consequences for the human species as a whole. For example, if it leads to a loss of valuable genetic diversity, which is the motor of evolution and has the effect of protecting a species. There is a dilemma here between individual and collective interests. If every individual pursues optimal health and that leads to less genetic diversity, the human species as a whole could become less 'healthy'.

for example, Gyngell et.al., 2017). Tests could be carried out before and during the pregnancy and in the genetically modified child to detect any unintended harmful effects from the genome editing. That raises the question, however, of what measures could be taken if any such effects are found – a question that could create serious dilemmas at every stage (before, during and after pregnancy). If, before the pregnancy, some unintended off-target mutations with uncertain effects were found in an embryo, would it then be transferred to the womb? What if the biological parents and doctors disagreed on this point? Or what if, during the pregnancy, it was found that there were unintended mutations in an entirely different gene in the foetus and the only possibility of preventing possible harmful consequences was not to allow the child to be born? Or take the case of a child whose genome has been edited and who suffers serious health problems at a certain age: would it then be possible to establish that they were caused by the genome editing of the embryo? And if that appeared to be the case, the question is whether that child should be allowed to procreate (without using reproductive technology), having regard to the health of his/her children and subsequent generations. The question of responsibility and liability for harmful, unintended effects from human germline editing is complex because those effects might only appear later in life, or even in later generations. Who would then be responsible? It might no longer be possible to hold accountable the doctors, the prospective parents or the scientists who chose to edit the heritable DNA because by then they have reached an advanced age or are dead.

Many of the precautionary measures that could be taken would be stressful for the children who result from the clinical research, their parents, the researchers and others. An important question in the public dialogue is, therefore, what precautionary measures should be taken in research from which genetically modified children are born? In light of the irreversible and intrusive nature of the targeted modification of children's genes, the procedure is often subject to strict requirements, and there are calls for the adoption of precautions. For the public dialogue, it is important to consider what safety and precautionary measures need to be taken, what potential dilemmas there are, and whether the suggested safety and precautionary measures are desirable and feasible.

3.3.3 Research in an international context

Scientific research into genome-editing technologies like CRISPR-Cas9 is conducted in an international context. This can enhance scientific progress, as scientists build on the results of each other's research and work together in international research groups. At the same time, this global context is also competitive. Countries, scientists and research groups compete to be the first to

achieve scientific breakthroughs and to patent the results. For example, since the development of CRISPR-Cas9, there has been a continuing patent dispute in the United States between the Broad Institute and the University of Berkeley (see, for example, Ledford, 2016). Competition can also create an incentive for scientists to break rules or ignore the existing consensus, as in the case of the Chinese researcher who, in contravention of international guidelines and the general consensus, modified the heritable DNA in embryos, from which two babies were born.

Laws and regulations on what scientific research is or is not permitted, and on the conditions that are attached to research, also differ between countries. Research into the modification of the human genome is no exception (Ledford, 2015). These differences can lead to *ethics dumping* and *moral free riding*. With *ethics dumping*, where researchers avoid the restrictions or prohibitions on particular research in their own country (for example, because it is regarded as risky or morally questionable) by moving to another country where there is no regulation or the rules are less strict.

Moral free riding is the situation where a country prohibits certain high-risk or ethically questionable research, but uses and profits from the results of such research. In the context of modifying hereditary DNA, for example, this creates a dilemma if laboratory research or research with humans is deemed too risky or ethically problematic in the Netherlands, but is permitted in other countries. The question then is whether it is acceptable to use treatments developed based on that international research.

3.3.4 Summary: the dialogue on human genome editing must also address research into the modification of DNA of future persons

The question of whether, and if so when, the modification of the DNA of future persons is acceptable cannot be seen in isolation from any research process that precedes the development of the relevant applications. One aspect of that research is that children with modified DNA will inevitably have to be born in order to gain an understanding of the risks and the long-term effects. For the purposes of the public dialogue, it is, therefore, important to clearly explain the following:

- that at some point, a balanced decision will have to be made on whether or not to conduct research that leads to children being born with modified DNA;
- that this is a complex issue that requires weighing up risks and benefits, which are uncertain and partly unknown, for the future child and his or her

- descendants, as well as the benefits and risks for prospective parents who could thereby have a healthy child that is genetically related to them;
- that how this decision is made can depend on different convictions and interests, and it is not clear who should have the final say;
 - that the safety and precautionary measures that could be taken in relation to research with humans can be burdensome and raise ethical questions;
 - that research takes place in an international context.

3.4 Domain of application in practice

In sections 3.2 and 3.3, we discussed some of the questions that arise with regard to research on genome editing in the laboratory or with humans. Here, we look at the questions that arise in connection with the application of technologies in practice. These questions are related to the consequences of germline genome editing for individuals, society and humanity in general. They include questions about the consequences of modifying DNA of future persons for social relationships, the future of reproduction, identity and human dignity.

3.4.1 Interpretation of terms used in the context of genome editing

One reason for permitting or investigating germline genome editing that is mentioned in every study and advisory report is the possibility of preventing serious, heritable disorders by removing the hereditary predisposition to them from the genome of an embryo that could grow into a child. This possibility could have benefits at both the individual and the collective level. It would give prospective parents the chance to avoid passing on heritable disorders to their children, with the result that these disorders would occur less often. This has benefits for public health and, possibly, also in terms of health-care costs.

However, terms such as ‘treatment’ or ‘prevention’ of disease are more ambiguous in the case of germline genome editing than with ‘regular’ medical treatments (Nuffield, 2018). The point is that this process concerns persons who do not yet exist, and perhaps never will exist, depending on the availability and success of genome-editing technologies to modify the embryo (Nuffield, 2018, p. 71).³⁷ In other words, germline genome editing does not ‘prevent’ a heritable serious disease *in* a child, but prevents a child from being born with that heritable disease. The

37 ‘We have to take care when applying categories such as “therapy” and “enhancement” (and also prevention) to the anticipation of people who do not yet (and may never) exist. What we are talking about is bringing about people with these characteristics, not changing the characteristics of people who already exist. The fact that they will exist at all may, in fact, depend on whether the intervention is permitted’ (Nuffield, 2018, p.71).

'treatment' is, therefore, not performed primarily on the future child, but on the prospective parents, for whom the technology represents an additional chance of having a healthy child that is genetically related to them (Nuffield, 2018, p. 26).

The fact that terms such as 'treatment' and 'prevention' are not unambiguous when applied to germline genome editing also makes it difficult to determine precisely who benefits from the use of genome-editing technologies to modify the DNA of future children. It gives prospective parents with a predisposition to a heritable disease a chance to have their own healthy, genetically-related child, and frees them from their pathological genes, thus increasing their reproductive options and autonomy. What is less evident is whether, and if so to what extent, the genetically modified child (that is born without the disorder) also benefits from the modifications to his or her DNA. Accordingly, regular medical terms such as 'treatment, prevention and eradication' of disease will have to be used with care in the public dialogue. The discussion will also have to be about the scale, the nature and the legitimacy of the benefits of germline genome editing, and who actually benefits.

3.4.2 Importance of prior knowledge of a person's genetic predisposition

In practice, the possibility of preventing diseases from being passed on to offspring with genome-editing technologies does not mean that every instance of those diseases can be prevented. A crucial requirement for making the choice to modify the DNA of a future child is prior knowledge of the existence of a predisposition to a disorder (Nuffield Council on Bioethics, 2016, p.45). Prospective parents must know that they have a genetic predisposition to a heritable disease if they are to decide not to proceed with a natural pregnancy. After all, for the time being, the procedure of genetic modification will have to include IVF. Some prospective parents have that knowledge because they themselves have a heritable disorder; others might not be ill, but know that they are possible carriers of a disease based on their family history. There are also diagnostic and screening tests that can reveal genetic risks and whether a person has the status of a carrier. The importance of prior knowledge is discussed further in box 5.

Box 5 Knowledge of carrier status

In one in every 150 couples who are not ill, the man and the woman are genetic carriers of the same recessive disorder without knowing it.³⁸ In the case of the recessive heritable disorder cystic fibrosis, for example, an estimated one in every 30 Dutch persons are carriers of an abnormality in the CFTR gene. If a child inherits an abnormal gene from both parents, it will have cystic fibrosis. If the child inherits only one abnormal CFTR gene, the child will be a healthy carrier. Consequently, when both the man and the woman in the couple are carriers of a recessive disorder, there is a 25% chance that their future child will have the disorder, and a 50% chance that, like themselves, it will not have the disorder but will be a carrier, and a 25% chance that it will not have the disorder and will also not be a carrier. In practice, many prospective parents do not know in advance that they are carriers of a disorder, and often only discover that they are after the birth of a child with the disorder or, during the pregnancy, following a prenatal genetic test (such as chorionic villus sampling). To prevent transmission of the disorder in the event of another pregnancy, the couple can choose embryo selection or, potentially, modifying the DNA of the embryo (which is not yet possible). In both cases, an IVF programme would be required. If they choose for a 'natural' pregnancy, the chance that the child will not be ill is 75% (with a 50% chance that the child will be a carrier of the disorder). To exclude the possibility that both parents (who are not ill) could pass a defective gene on to their child in the first pregnancy, they will have to undergo a preconception test for a recessive genetic condition to learn whether they are carriers of a disorder.

A substantial proportion of heritable complaints are caused by spontaneous mutations in the DNA: mutations that have not previously been found in the parents' heritable material, but which arise spontaneously during the embryo's early development.³⁹ In those cases, there might not be prior knowledge, and genome editing would not be an option.

38 See <https://erfelijkheid.nl/kinderwens/loop-ik-kans-om-drager-te-zijn>

39 In other words, a person with a heritable disorder that is the result of spontaneous mutations has not inherited it from his or her parents, but can pass it on to his or her offspring.

The extent to which heritable disorders can be prevented by altering a person's genetic predisposition to those disorders, therefore, depends on various factors.

They include:

- the supply, funding and availability of genetic tests;
- the supply, funding and accessibility to the procedure of embryonic genome editing;
- the decisions made by prospective parents on whether to make use of the available options.

During the public dialogue, it is, therefore, important for people to discuss those factors relating to the practice and procedure of using genome editing to modify the DNA of a future child and how those factors influence the planning of a pregnancy.

3.4.3 Uncertainty about genetic modification with genome-editing technologies

Heritable disorders are caused or influenced by various types of genetic defects (see the box in section 1.3). Diseases are sometimes caused by a change in a single gene, but far more often they originate in a combination of errors in multiple genes, together with environmental factors. Accordingly, different types of modifications with genome-editing technologies are needed to repair the various types of genetic defects. The accuracy, effectiveness and efficiency of technologies can differ greatly depending on the type of modification, and those differences affect the suitability of genome-editing technologies for preventing or reducing the prevalence of particular genetic diseases (see, for example, COGEM & Health Council of the Netherlands, 2017; Nuffield Council on Bioethics, 2016).

For every type of modification, there is still uncertainty about whether genome-editing technologies can actually be used, and the chance of success can also vary greatly from one application to another. According to most scientific reports, making a single targeted genetic modification is a technologically realistic option, but doubts have been expressed about the possibility of simultaneously making multiple modifications. The extent to which genetic properties and disorders can be influenced with genome-editing technologies also depends heavily on the prevailing knowledge of genetics. To make targeted DNA modifications with genome-editing technologies, the relevant genes first have to be identified. That calls for knowledge about which genes or combinations of genes contribute to which disorders, traits or characteristics.

Alternatives to genetic modification

Public surveys show that for many people the acceptability of genome editing depends on the intended changes and their purpose (see section 2.3). For that reason, it is important to devote attention in the public dialogue to the extent to which genetic traits can be influenced by genome-editing technologies. What technological obstacles have to be overcome before it could become possible? What traits might be affected by germline genome editing? In other words, there are a number of factors to consider in making the choice between modifying DNA in embryos and the alternatives.

A question often raised in discussions of germline genome editing is what added value it provides compared with existing alternatives through which prospective parents with a heritable disorder, or who are carriers of one, can have a healthy, genetically-related child. Embryo selection, for example, is often mentioned as an alternative method for preventing serious heritable diseases (see box 2 on page 23).

On the question of the added value of DNA modification in an embryo compared with embryo selection, a distinction is often made between:

- cases where DNA modification is the only option for parents to have a healthy, genetically-related child, because embryo selection is not an option.
- cases where DNA modification and embryo selection are both possible, and the question is which option is preferable.

There are few instances when germline genome editing offers prospective parents with a predisposition to a heritable disease the chance to have a healthy, genetically-related child, but embryo selection does not (see, for example, COGEM & Health Council of the Netherlands, 2017).⁴⁰ Because these situations are rare, the question is what a fair distribution of the available research funding would be: how much money should be spent on research to develop genome-editing technology to modify heritable human DNA when only a limited number of prospective parents would use it? The discussion would shift if it were technically possible to make more than one genetic modification in an embryo's DNA. In that case, germline genome editing might have greater value than embryo selection, because germline genome editing could reduce the risk of polygenetic and multifactorial disorders.⁴¹

40 For example, this would be the case if all of the embryos that could be created with the reproductive cells of the prospective parents would always possess the disease; for instance, if both prospective parents have a recessive heritable disorder (such as cystic fibrosis), or if one or both of them is homozygous (has two identical copies of a gene) for a dominant heritable disorder (such as Huntington's disease).

41 With embryo selection, a selection is made from embryos whose genome was created by natural recombination. The more a selection is made on the basis of the presence of multiple desired gene variants, the smaller the chance that there will be an embryo among them that possesses all of the desired variants. In other words, by making a targeted change in an embryo's DNA, an embryo can be created with a genome that could never realistically have been created by natural recombination.

In cases where embryo selection and germline genome editing could, in theory, achieve the same objective (namely, giving prospective parents the chance of having a healthy, genetically related child), there is no simple answer to the question of which option would be preferable. A number of considerations would play a role in providing the answer. For example:

- Scientific considerations regarding the likely chance of success of embryo selection (given the number and quality of the available egg cells) compared with that of modification of the DNA of an embryo (given the specific modification that has to be made in the DNA).
- Whether there is a morally relevant difference between embryo selection and modifying the DNA of future children.
- Whether no embryos would be lost during the procedure to modify embryonic DNA, or fewer than with embryo selection.
- Whether modifying the DNA of an embryo would yield additional benefits for future generations because the modification would reduce the chance of a person being a carrier.
- How such advantages weigh up against the extra risks (of off-target effects, for example).
- The irreversibility of changes made in heritable human DNA and the fact that they would be passed on to every future generation.

These are all complex, moral considerations, in addition to which there is also considerable uncertainty about the safety and chance of success of future treatments.

Embryo selection is currently the most immediately imaginable alternative to germline genome editing. However, progress is also being made in developing better treatments and improving care for patients with a heritable disorder, thereby enhancing their life expectancy and quality of life. In recent years, there has also been a lot of research into somatic gene therapy, where modifications that will not be transmitted to offspring can be made in the DNA of an existing person's cells. If somatic gene therapy makes it possible to treat or cure heritable diseases once a child is born, it could be a realistic alternative to modification of DNA in an embryo in terms of minimising the consequences of the transmission of those diseases.⁴²

42 For successful somatic gene therapy, the DNA of a large number of cells have to be altered simultaneously. Most of the progress made in recent years has been achieved in the treatment of blood and autoimmune diseases, because for these disorders it is possible to cultivate large numbers of genetically modified cells in the laboratory (i.e., outside the body). In the process, stem cells are taken from the bone marrow (these are the cells from which red and white blood cells are formed). After the cells have been genetically modified, their division is stimulated, thus creating large numbers of healthy cells, which can then be implanted into the patient to replace his or her unhealthy (non-genetically modified) blood or autoimmune cells.

Weighing the modification of the genes of a future child against existing, or future, alternatives⁴³ is, therefore, connected with a number of considerations. Views can therefore differ on the added value of modifying the DNA of embryos, and about its utility and necessity. The question of the added value of modifying the DNA of embryos compared with alternatives, and the values and considerations that play a role in assessing it, therefore has to be considered in the public dialogue.

3.4.4 The distinction between desirable and undesirable applications of germline genome editing

Technologies for germline genome editing raise the question of what we are or are not willing to permit in terms of the modification of the DNA of future children and generations. There is also discussion of what the criteria should be and who should decide in specific cases. The relevant considerations could vary for different types of application.

With modern genome-editing technologies, cuts can in principle be made anywhere in the DNA and numerous heritable traits can, therefore, be influenced. Various types of application can be distinguished according to the purpose of the modification of the DNA. Many scientific and ethical reports make the following distinction (or a similar one) between technologies:

- To prevent the transmission of serious heritable monogenetic disorders, where the disease is caused by an abnormality in a single gene (such as Tay-Sachs disease or cystic fibrosis).
- To prevent the transmission of heritable monogenetic disorders that are less life-threatening (such as congenital deafness).
- To reduce the chance of disorders with a partially genetic cause (such as diabetes or Alzheimer's disease).
- To make changes that will improve certain traits or characteristics (such as appearance, intelligence or athletic performance) in the future person. This is also referred to as human *enhancement*.⁴⁴

Accordingly, this categorisation makes a distinction between medical and non-medical applications. A further distinction is made among the medical applications between serious and less serious disorders, and between reducing the chance that a person will have a disease and preventing the disease. At the same time, those who use such a classification always stress that there is no clear distinction

43 Including the alternative of not having children, having a child that is not entirely genetically related, or accepting the risk of having a child may have a serious genetic disorder.

44 It is also theoretically possible to implant genetic variants that do not normally occur in the human genome.

between medical and non-medical applications, between normal natural variation and abnormal disease, or between serious and non-serious disorders (see also box 6).

Nor is there any common definition of what constitutes a disease, and hence what can or should be treated, in every culture or society. The boundaries are constantly being redrawn (Danish Council on Ethics, 2016, p 6).⁴⁵

Public surveys show that many people regard modification of DNA of future children to prevent serious genetic defects from being passed on to a couple's own children as more acceptable than applications aimed at enhancement (see section 2.4). Reports on the science and ethics of the technology and advisory reports also generally assert that there are stronger arguments in favour of applications designed to prevent children from being born with serious heritable diseases than for enhancement purposes. Applications for the purposes of enhancement raise various issues and reservations (see, for example, German Ethics Council, 2019, p. 23,24)

45 'Sometimes it is difficult to draw a sharp line between diseases and the outer limits of normal. Consider this: Is it a disease having protruding ears or being very short? While this is debatable, we nonetheless treat both conditions in hospitals. The boundaries of disease are not fixed. They are continuously being drawn and redrawn in different cultures with different opportunities for treatment.'

Box 6 Distinction in applications is not clear

An example of a disorder for which it is difficult to make a clear distinction between medical and non-medical treatment is *schisis* (cleft lip). This is a congenital disorder whose seriousness and susceptibility to treatment can vary greatly. It depends on the precise situation: is there only a split in the upper lip or does it extend to the palate, the uvula or the jaw? Whereas preventing a split in the upper lip is primarily cosmetic, preventing a split in the jaw could fall into the medical domain because it can have serious consequences for a person's health.

The American IVF clinic 'Genomic Prediction' provides another example from reproductive practice. The clinic offers an embryo selection procedure to establish, based on a genetic screening, whether an embryo has a high risk of 'intellectual invalidity'. On its website, the clinic explicitly states that it is not possible to select an embryo with a greater chance of high intelligence, because it only screens for the risks of a disorder. This is its way of making a distinction between desirable applications (designed to prevent a disorder or an increased chance of a disorder) and undesirable applications (non-medical applications aimed at selecting desired characteristics). The term 'intellectual invalidity' assumes the existence of a clear bottom line where normal natural variation in intelligence crosses over into a disorder, which would justify preventing or treating it. But that boundary is difficult to establish, so it is questionable whether the clinic genuinely selects solely based on possible 'disorders'.

One consideration, therefore, is the fact that the balance between benefits and risks is often less favourable with applications for human enhancement because there is no medical need for them. There are also more ethical concerns about applications for enhancement, such as respect for human dignity and autonomy. This might be the case if parents can change their future child in such a way as to increase its predisposition to developing certain characteristics or personality traits that meet their own wishes and objectives as parents.

This could impair the child's dignity and freedom because it would be highly instrumentalised: the child becomes a product of the wishes of his or her parents, and is, therefore, hampered in freely determining and pursuing his or her own goals in life. On the other hand, it is open to discussion whether every form of genetic

improvement infringes on a person's dignity and freedom or whether genetic improvements could, in fact, possibly help future persons to achieve some of their personal goals in life (see, for example, German Ethics Council, 2019 p. 23/24, or Savulescu & Bostrom, 2009).

Another concern is that growing use of applications for genetic enhancement could have more far-reaching consequences for the character of society and relationships within it. If, for example, only certain privileged groups have access to such enhancements, it could lead to wider inequality. It could also lead to a shift in power relationships between the current generation, which makes decisions about genetic traits, and the future generations that are genetically altered. The character of a democratic society as a community of members with equal rights and duties could be eroded.

But intragenerational relationships could also become strained. Take, for example, the relationship between brothers or sisters in the same family, where some have been genetically modified and some have not? Or the question of who decides within a family which genetic properties are desirable or undesirable, and what interventions are justified to create or prevent them? In some countries, for example, the preference for having a boy is so great that women are sometimes forced to have an abortion if they are expecting a girl. The availability of a technology to modify genetic properties could lead to new forms of compulsion and coercion around pregnancy and reproduction.

Finally, the concept of 'naturalness' can play a role in assessing enhancement applications. Whereas preventing heritable disorders is actually designed to repair a genetic defect and restore the natural original variant (with Huntington's disease for instance, see section 1.2), enhancement applications could be aimed at deviating from the natural situation or variation.

In other words, there is a broad consensus that the acceptability and desirability of germline genome editing depends on the purpose for which the genetic modifications are made and that there is a morally relevant distinction between medical applications and applications for human enhancement.

However, in practice it is difficult to draw a clear line between desirable and undesirable applications, partly because the commonly made distinctions, for example between normal variation and disease or between medical and non-medical, have only limited value as guidelines. The discussion also frequently concerns the 'chance of having a disorder' rather than an existing disease. Furthermore, various considerations, values and arguments also play a role in assessing the acceptability and desirability of an application. To address them

adequately in the public dialogue, the dialogue should not focus on establishing which applications (or categories of applications) are desirable or otherwise, but rather on discussing the values, considerations and arguments that do or should play a role in making that assessment.

3.4.5 Considerations relating to ethical principles and concepts such as human dignity and identity

In addition to the biological and medical consequences of intervening in the DNA of a future person, there is the issue of the consequences for his or her identity, rights and dignity. An important question is whether human dignity, and an individual's interests and rights – such as the right to an open future – will be at risk if his or her genome is specifically designed using genome-editing technologies.

Terms such as 'right to an open future', 'identity' and 'human dignity' are often used in discussions about the targeted modification of the genes of future persons and the laws and regulations on the subject. Although these are important concepts and ethical principles, they are often defined and interpreted differently in the discourse on targeted modification of future persons. For example, the explanatory memorandum to the Dutch Embryo Act raised the question of whether respect for an individual's dignity meant that a person had the right to inherit a genetic pattern that has not been altered through targeted human intervention, or whether it means that modification of a person's DNA to prevent him or her from inheriting a heritable disorder actually accords with that principle (Kamerstukken II, 2000/2001, 27 423, no. 3, p.45). The Health Council of the Netherlands takes the view that removing a serious inhibiting disease, in fact, benefits a person's dignity and his right to an open future. The same applies to the dignity of prospective parents, who are able to avoid passing on a serious heritable disorder to their offspring (see, for example, COGEM & Health Council of the Netherlands, 2017).

In contrast, Van Beers argues that this view places the emphasis solely on the individual dimension of human dignity (protection of individual freedoms), while human dignity also has a collective dimension (protection of our humanity, which forms the basis of these rights)(Van Beers, 2019). The prohibitions and limitations on intervening in the human genome contained in human rights treaties are also aimed at protecting the collective dimension of human dignity.

Identity

The notion that DNA is closely connected with our identity is widely supported. We can even find examples of this in our everyday language, for example when DNA is described as 'the blueprint for life' or in marketing slogans such as 'good service is

in our DNA'. This idea is also to be found in national and international legislation, regulations and treaties. The Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), for example, states that the human genome underlies the fundamental unity of all members of the human family (Article 1). European legislation on clinical research contains a prohibition on tests 'which result in modifications to the subject's germ line genetic identity.' (Regulation (EU) 536/2014, Article 90).

Simultaneously, there is considerable debate about the precise relationship between the human genome and identity. One criticism of the term 'genetic identity' is that it wrongly assumes that human identity is entirely embodied in the DNA.⁴⁶ According to the German Ethics Council, it is, therefore, important to reflect on what role the genome plays, actually and symbolically, in our thinking about what it means to be a human being. Without giving way to simplistic assumptions, such as the idea that identity is entirely embodied in the DNA, on the one hand, or the idea that the genome is merely a random biological system component, on the other (German Ethics Council, 2016, p.5).⁴⁷

The Nuffield Council on Bioethics refers in this context to psychosocial identity. In that sense, identity depends far more on how individuals perceive and shape their identity within their social context (Nuffield Council on Bioethics, 2018). Based on this concept of identity, the impact of the modification of a person's DNA on his or her identity has to be interpreted in terms of the consequences for the psychosocial context in which that person perceives and shapes his or her identity. Precisely because the targeted modification of the genome of a future person can have an influence on the unique embodiment of a person (and experience thereof),⁴⁸ on social relationships (such as the parent-child relationship), and public relationships, the question of the consequences of modification for identity remains relevant.

In the public dialogue, it is, therefore, important to discuss the precise relationship between terms such as human dignity and identity and interventions in the human genome. In discussing the question of whether modifying heritable human DNA is or could be an infringement of human dignity and identity, attention should be devoted to both individual and collective considerations. Individual considerations are the consequences for those directly concerned, their freedoms and their dignity. The collective considerations that need to be discussed are the consequences for social relationships, public relationships and what it means to be a human being.

46 Such a vision of identity is known as genetic determinism, or genetic essentialism.

47 'A question of special relevance in this context is the role which the genome assumes both de facto and symbolically in the understanding of being human – without either succumbing to the simplifying assumptions of genetic determinism or qualifying the genome as a random biological system component.'

48 See also Nuffield Council on Bioethics, 2018.

3.4.6 The impact on future generations

The perspective of those directly concerned is important and must be explicitly heard in the public dialogue. However, that perspective sometimes fails to take account of the fact that modifying the DNA of future persons can have unforeseen consequences for entire generations: for their health, dignity and identity and for the society in which they live.

Consent

Informed consent is an important principle in medical care, one that safeguards a patient's autonomy. A medical intervention may generally only be performed if the patient has given *consent* based on a free, *informed* decision.⁴⁹ With genome editing to modify an embryo's DNA and other reproductive technologies relating to future persons, it is, by definition, impossible for that consent to be given. In situations in which informed consent is not possible, the criterion of *assumed consent* is often adopted. Medical intervention could then be justified if it is reasonable to assume that a future person would consent to it.

The question is how informed consent relates to the possible applications of genome editing to modify embryonic DNA (see also 3.3.5).

From the perspective of future generations, the scope of assumed consent is unclear, since the genetic modifications that are made with a single germline intervention are then passed on to all of the descendants.

Social diversity

Because modifications to heritable traits continue into future generations, they can also have consequences for the human species as a whole. If they lead to the loss of genetic diversity, for example. Or if modified genes unintentionally spread throughout the gene pool. Genetic diversity is the motor of evolution and protects the species. In that context, there is a dilemma between individual and collective values. If every individual pursues optimal health and this leads to less genetic diversity, the human species as a whole could become less 'healthy'. This is not just a biological issue, but also a social issue. Is a society full of 'better people' also a 'better society'? That is dubious. Whether, and if so, to what extent the genetic modification of future persons could lead to a loss of genetic and social diversity depends on the reasons for application, and the scale on which it is applied.

Because the consequences of modifying the human genome can affect individuals, future generations and the human species as a whole, the subject concerns

⁴⁹ There are exceptions to this. For example, in emergencies, or if a patient is not of sound mind, or if non-intervention creates an acute public-health risk.

everyone. For the public dialogue, therefore, considerable attention has to be devoted to reaching, engaging and listening to the largest possible number of people. It is also important to find a way of allowing future generations to have a voice in the dialogue.

3.4.7 Attention for the broader public and social consequences

In addition to the consequences for those directly involved and the possible impact of modification of hereditary DNA on future generations, it is important to discuss the broader potential consequences of germline genome editing for society. The precise repercussions are still uncertain, but history shows that technology often has major consequences for society and that technology and morality influence one another. For example, the introduction of the anti-conception pill not only had an impact on women's emancipation – by giving them more control over whether they became pregnant – but also on sexual morality. The introduction of anti-conception made it possible to separate sexuality from reproduction, thus increasing acceptance of sex for other purposes and prompting a change in views towards homosexuality (Kundina & Verbeek, 2019).

Genome editing to modify the DNA of future persons is not a neutral technology, and consideration of its application will in time influence standards and values. The existence and availability of the possibility to intervene in the DNA of future generations will have consequences in terms of how individuals and society look at pregnancy, reproduction, sickness and health, and the associated norms and values. So even if its application is seen as a medical success (if the desired DNA modification is made, the heritable disorder does not occur and no unintended changes are made), the introduction of the technology could still have unintended consequences at the level of the society. Although such broad social consequences are difficult to predict, it is important to explore and discuss them in the public dialogue. Techno-moral future scenarios, which expose moral and public dilemmas and changing patterns in public values, could play a role in that discussion (see part 2 of this report). They could stimulate discussion and help to create empathy with possible future situations. In the rest of this section, we briefly discuss the possible consequences of germline genome editing for public and social relationships.

Inequality

One concern about the possibility of directly modifying the DNA of future children is that it could further reinforce existing socioeconomic inequality and create new forms of inequality (see, for example, Olson (ed.), 2016). This might be the case, for example, if it is mainly people with a higher socioeconomic status who enjoy the benefits because they have better access to specialised reproductive treatments. It

might also be easier for them to travel abroad for medical or enhancement treatments that are not available in the Netherlands.⁵⁰ The international context, therefore, also determines the extent to which this inequality will occur. The advantages that these children possibly already enjoy through their socioeconomic status will then be further reinforced because they will also have a genetic advantage over their peers. This could lead to new social or genetic classes.

On the other hand, genome-editing technologies could be consciously used in an attempt to reduce inequality, for example by making certain interventions available to prospective parents with a lower socioeconomic status. The scale of the consequences for social inequality if germline genome editing is permitted depends – in part – on the reasons for which the technology is made available, the global scale on which it is used and how the technology is used.

Concerns about stigmatisation

Another concern is the possible stigmatisation of people with a genetic disorder if there is an intervention available that can prevent the transmission of that disorder. This concern also extends to children who are later born with that disorder. If such interventions are applied on such a scale that they have a significant influence on the number of people in a society with a particular disorder, it will have an influence on these people's communities. They will have fewer fellow sufferers, for example. Growing attention to preventing a heritable disorder could also have consequences for the quality and availability of care and other facilities for these people. If there are fewer people with a particular genetic disorder, awareness of, familiarity with and social acceptance of people with this disorder could decline (Nuffield Council on Bioethics, 2018, p.84).

Even if the intervention is not used on a large enough scale to have a noticeable impact on the number of people with a particular disorder, there are those who say that making genome editing available to prevent or reduce the chance of certain heritable disorders or traits reflects a negative attitude towards those disorders (Nuffield Council on Bioethics, 2018, p. 84). It confirms the undesirability and preventability of such disorders. This could have an impact on how the society looks at and deals with people with particular genetic disorders or properties, their parents, or prospective parents with a heightened genetic risk.

The perspective of people with a heritable disorder plays an important role in the discussion of the public consequences of the genetic modification of future persons. In that context, it has to be noted that groups that represent patients are

⁵⁰ This is also called 'medical tourism'. It is known that other technologies in reproductive medicine such as cell donation and commercial surrogacy can often have negative consequences for the less well-off population in the 'tourist destinations' (see, for example, Verhoef, 2019).

heterogeneous, as are the diseases that they represent. Attitudes towards germline genome editing will differ both between and within the groups of people with different heritable disorders. It is important to avoid assuming that everyone in the group of 'people with a heritable disorder' experience life with their disorder in the same way and share the same attitude towards the possibility of preventing the disorder from being passed on to their descendants. The impact of a heritable disorder on a person's quality of life and the extent to which people see the disorder as part of their identity can vary greatly – both from one disorder to another and from one person to another. There is also often a tension in the attitudes of the representatives of patients. They fight hard for the eradication of 'their' disease, but simultaneously campaign for social acceptance of it. Like everyone else, they want to fully participate in the community and society (Olson (ed.), 2016, p.4).

Concerns about stigmatisation are not confined to those who have a heritable disease, but also extend to physical features, for example. Ethnic minorities could alter their children's DNA in order to make them look more like the majority of the population. As with people with a disorder or a disability, this could adversely affect the visibility and acceptance of people who look 'different'.

Shifting public and social values and standards

The possibility of modifying heritable properties and disorders can have consequences for public and social standards, for example with regard to sickness and health and what disorders and imperfections should be prevented. This could cause a shift in what are regarded as normal/usual choices with respect to reproduction. It could also create certain social expectations (Nuffield Council on Bioethics, 2018, p. 80). Although germline genome editing gives prospective parents new liberties in the field of reproduction, the fear is that the new social expectations could create compelling pressure to adhere to them and the liberties of prospective parents will, in fact, decline. For example, what would be the consequences if parents choose to have a child with a serious heritable disorder that could have been prevented with genome editing of the embryo? Will the medical care the child needs be paid for from public funds? And to what extent will future children blame their parents if they are born with a disorder that could have been prevented with genome editing?

As these examples show, the possibility of intervening in the DNA of future persons has a range of public consequences, for example in terms of public and social relationships, where there are concerns about stigmatisation and inequality. But also for the practice, values and norms surrounding pregnancy, reproduction, and health and sickness in general. The public dialogue must, therefore, address not only the question of whether or not individual applications of germline genome editing are acceptable, but also the broader social implications.

3.4.8 Summary: the role of broader social consequences in the dialogue on germline genome editing

The consequences of using genome-editing technologies to modify the DNA of future persons are uncertain and unpredictable. They depend greatly on what applications become available, and how. A lot is still unknown about that. The main challenge for the public dialogue lies in reviewing the consequences for individuals, society and the human species, and for various practices such as reproductive health. It is, therefore, important to explore the following uncertainties and confusions in the dialogue:

- Terms such as ‘treating, preventing, eliminating’ disease are not unambiguous in the context of germline genome editing because it concerns non-existent persons and their descendants. It is, therefore, unclear precisely what the advantages and disadvantages of modifying the DNA of future children are, and for whom.
- What form will the practice of human genome editing take? To be able to use genome editing in practice, people must have prior knowledge of their own genetic predisposition, for example by undergoing tests to determine whether they are carriers of a disease. At present, genome editing also requires an IVF procedure.
- It is still uncertain what modifications will be possible in the future with genome-editing technologies. This is connected with biological aspects and technological obstacles, but also, for example, with the practical feasibility and desirability of extensive screening of prospective parents and embryos, including the capacity for IVF.
- The added value of modifying embryonic DNA compared with alternatives such as embryo selection will be interpreted differently by experts and stakeholders, and depends on underlying considerations.
- It is difficult to make the distinction between desirable and undesirable applications. Instead, there could be a discussion of the underlying values and considerations behind such a distinction.
- Discussions about the modification of DNA embrace abstract principles, such as identity and human dignity. These concepts often have a lengthy tradition in the debate about genetic modification of future persons. The dialogue should explore what these terms mean in the context of the modification of human genome editing.
- The dialogue must address the consequences for future generations.
- Social consequences of germline genome editing, such as stigmatisation, inequality and changing norms and values concerning health, sickness and solidarity, must also be discussed.

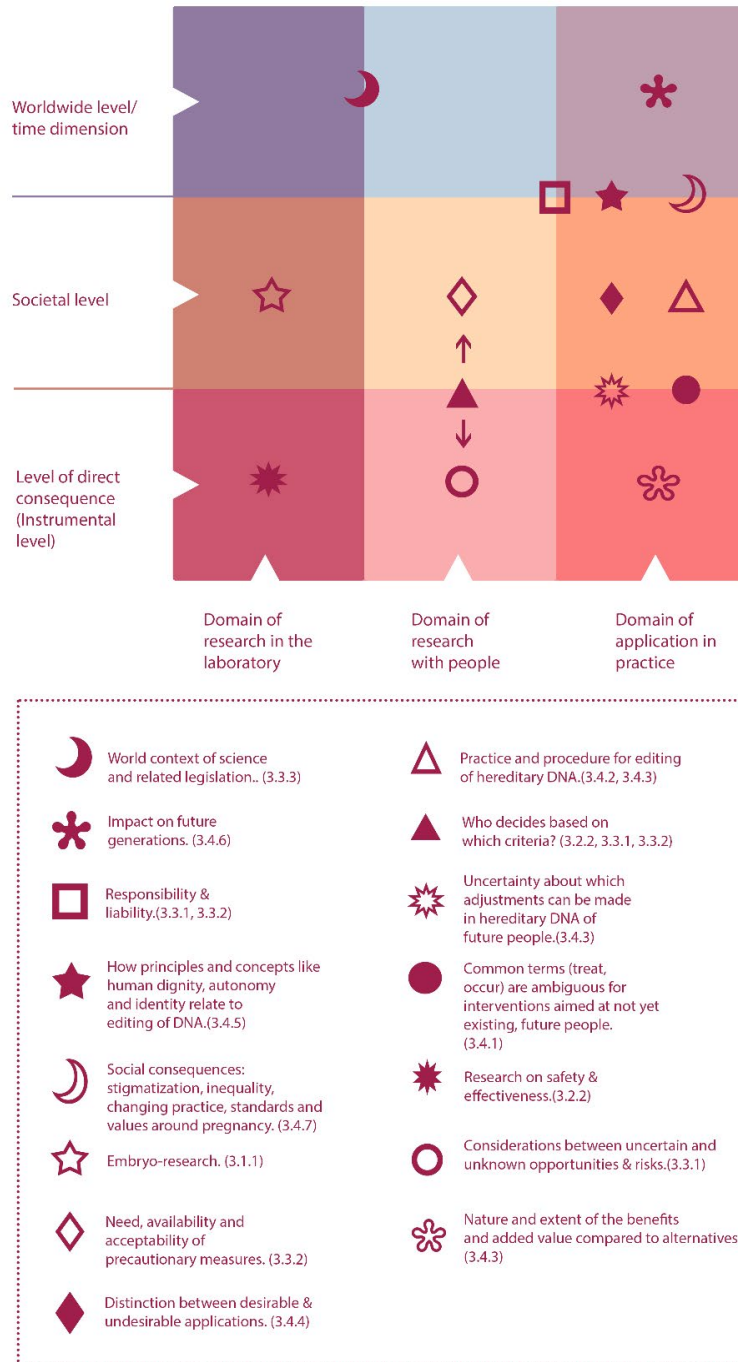
Despite the complexity of the subject, it is important that all of these aspects are covered in order to have a fruitful public dialogue. The techno-moral future scenarios described in chapter 5 of this report can help in that.

3.5 Conclusion: dialogue with many levels and dimensions

The overview of ethical and social issues that we have presented in this chapter shows that there is still a great deal of uncertainty surrounding the scientific and technological developments and their consequences for individuals and society. The uncertainties cannot be easily resolved and call for thorough exploration in public dialogue. The issues discussed highlight the themes that need to be addressed in the public dialogue and identify the parties that should be involved in it. Figure 2 illustrates all of the issues discussed.

To provide a systematic overview of all the social and ethical issues involved, we divided them into three domains: the domain of *research in the laboratory*, the domain of *research with people* and the domain of *applications*. For the public dialogue, it is important to cover the issues that arise in each of the domains. Each domain in turn raises its own issues, considerations and questions at each of the three levels that we discussed in section 1.3 (the direct consequences, their embedding in society and broad social consequences, and the international context). Individual and collective considerations often both play a role.

Figure 2 Discussion of technology at different levels and in different domains



Source: Rathenau Institute

In the domain of *research in the laboratory*, what is important for the dialogue is not so much how specific genome-editing technologies work, but how to establish whether the technologies are safe and effective. Precisely when can we describe them as safe and effective, and what scientific and technological obstacles need to

be overcome? These are considerations at the level of the technology itself, the *instrumental level*. It is often thought that human embryos have to be created specifically for laboratory research into the application of genome-editing technologies to modify the heritable human DNA. What does this imply for the issue of creating embryos specifically for research, the protection of early life and for the donors of the semen and eggs? These are issues at the level of *social embedding*. What actions with human embryos do we as a society regard as acceptable? Finally, research into the use of genome-editing technologies to modify the DNA of future persons is not confined within national borders. Research is conducted in laboratories around the world and scientists share the results of their research in international journals and at conferences. The international context is, therefore, an important factor in the dialogue.

In the domain of *research with people*, there are also issues at all three levels. The research itself is initially aimed at determining the long-term effects and effectiveness of the technology. However, the technology can also have consequences for the human species as a whole, because it will inevitably lead to the birth of children whose heritable DNA has been modified, and those modifications will be passed on to all their descendants. Questions also arise about what risks and precautions we as a society regard as acceptable for clinical research. In that domain, the time dimension is a factor because unintended and possibly harmful consequences for future persons and generations might only emerge in the longer term.

The domain of *applications in practice* concerns, at the *level of the technology*, what applications are or are not possible, how we can assess and discuss them, and what possible alternatives there are. But the issue of the desirability of these applications and their social consequences (which we described in section 3.4) arises at the level of the *society*. Finally, the *global level* cannot be ignored. For example, reference is frequently made to the phenomenon of medical tourism. But many of the ethical principles cited in the debate, such as human dignity and identity, also relate to humanity as a whole.

Conclusion

In this chapter we have provided an overview of the ethical and social issues surrounding germline genome editing. We have shown that the issues encompass three domains and that the issues in each domain arise at different levels. In that context, there are both individual and collective considerations. This makes the dialogue both complex and extensive. In chapter 4, we make a number of recommendations for the form and content of the public dialogue, as well as ten lessons for conducting the best possible dialogue.

4 Lessons for holding a public dialogue

The modification of the genetic attributes of future children and generations affects everyone. Starting in October 2019, the ongoing discussion of the subject in the Netherlands is being given an extra stimulus to give everyone a chance to take part in the debate. A number of organisations, including the Rathenau Institute, have taken the initiative to hold a National Dialogue on Human Germline Genome Editing. The Ministry of Health, Welfare and Sport is subsidising the project, which was launched in January 2019 to facilitate and promote a broad public dialogue and the process of collective opinion formation. The aim is to reach the widest possible audience, inform the public of the issues and encourage people to discuss their hopes, wishes and concerns about germline genome editing and its broad social consequences. This report provides a guide to this national dialogue. At the end of 2020, the results and findings of the dialogue will be collected in a final report designed to inform political decision-making and policy formulation. The results will also be published in an accessible form for the general public.

As described in chapter 1, the discussion about genome editing is not new, but a broad dialogue is now urgent and relevant for the following reasons:

- The subject is topical: there were shocked reactions around the world at the news of the birth of the Chinese twin sisters, Lulu and Nana, whose heritable DNA had been modified using CRISPR-Cas9. This topic has been widely discussed both nationally and internationally. Numerous papers, reports and statements have been published and many articles have appeared in newspapers and magazines on the subject in the last few years (see chapters 2 and 3). There have also been a large number of symposia, conferences and other public events devoted to the subject.
- The public dialogue needs to have a wider scope: based on the findings in chapter 2, we conclude that there has still been no *broad* public dialogue in this country. Up to now, it is mainly the opinions of experts and opinion makers that have been heard. The discussion has generally also been devoted to technical and scientific issues. There has been far less attention to the specific possibilities, opportunities, risks, uncertainties and broader social consequences of genome editing, despite the important role of these aspects in the debate. It is a complex and controversial subject that embraces a wide range of social and ethical issues, which are not always explicit (see chapter 3).

- There has been a renewed discussion of the current laws and regulations and the reasoning behind them. The subject, therefore, touches on specific political and policy issues, such as the question of whether the Embryo Act should be amended.
- There is an evident political desire for a public dialogue on the subject and the current government wishes to take the results of that dialogue into account in the political decision-making (Rijksoverheid, 2017 pp. 17,18)

In a nutshell, the time is right and there is support for public dialogue in the Netherlands. But what is needed to conduct a good public dialogue? In this chapter, we discuss that based on ten lessons.

4.1 Requirements for a public dialogue

The Rathenau Institute has years of experience with public dialogues on emerging technologies that could have a major impact on individuals, groups, practices, social relationships and collective values.⁵¹ Building on that experience, in this chapter we present some general requirements for conducting a broad public dialogue. We conclude the chapter with ten specific lessons for holding the dialogue on germline genome editing (the modification of the DNA of future persons).

Public engagement

An important goal of public dialogue is to help members of the public to form an opinion on a subject that is not only complex, but also unfamiliar to many people. Accordingly, it is necessary to reach people and engage them in the subject and to allow them to inform themselves, to form an opinion and to exchange perspectives and arguments. Up to now, the debate about germline genome editing has been conducted mainly among experts. The general public has not really been involved. There have been some surveys of public opinion in the Netherlands and elsewhere. Although such research can provide a valuable impression of public attitudes, there has been no process of collective opinion formation.

Information about the broad consequences for individuals, society and humanity

To reach an informed opinion on issues connected with complex technology, members of the public must be able to inform themselves about the subject. They need information, not only about how genome-editing technology works or the

51 See, for example, the dialogues on nanotechnology (Hanssen, Walhout & Van Est, 2008); synthetic biology (Rerimassie & Stemerding, 2012); nuclear waste (De Vries et al., 2015); the energy transition (Van Est, Waes & De Vries, 2016); geothermal energy (Smink et al., 2017); or the combination of human and animal cells (Van Baalen, Gouman & Verhoef, 2019).

purposes for which it can be used. Members of the public also need to be informed about the current state of the technology and realistic issues that it raises, as well as potential consequences for themselves or others, for society as a whole, and for current and future generations, in order to enable them to reflect on the issues and consequences. A public dialogue must, therefore, foster a diligent, joint analysis of the broader social consequences of introducing technologies which can be used to modify heritable traits in future persons. Another aspect that needs to be considered is the question of who will enjoy the benefits or suffer the negative effects of the technologies. In chapter 3, we presented an overview of the questions, issues and uncertainties that the public needs to be informed about. With that information, citizens can make a well-considered decision on the desirability of germline genome editing. Using this information to draft techno-moral future scenarios and vignettes (for example, animations), will help the process of reflecting on the issues involved (see the second part of this report).

Clarity about the subject matter of the dialogue

In chapter 2, we explained that there is no consensus on what precisely is at stake with germline genome editing: the development of new medical treatments that could prevent a lot of suffering or the future dignity and identity of society and humanity, or perhaps both.

In the absence of agreement on that point, there is also disagreement, sometimes implicit, on what the subject matter of the dialogue should be and what questions, arguments and considerations it should cover. To some, it is more or less clear that germline genome editing could be acceptable in principle, and that the dialogue should, therefore, be about the *conditions under which* it can be applied in practice. Others have reservations or objections to germline genome editing *per se*, and, therefore, want to focus mainly on its desirability. Earlier public dialogues (for example, the dialogues on nanotechnology and on the energy transition) have shown how important it is that the outcomes are still undecided (Hanssen, Walhout & Van Est, 2008; Van Est & Van Waes, 2016). The question of what is at stake in the dialogue about germline genome editing, therefore, has to be covered in the dialogue, which should address both the fundamental desirability of germline genome editing and the conditions under which it could be applied (see also lesson 1 below). Members of the public must feel free to speak their minds on both subjects. Being able to do so will bolster their confidence in the dialogue.

Involvement of related themes

Closely connected with the debate on modification of the human genome is the question of whether it is acceptable to create embryos specifically for research. The interconnectedness of the two themes could make the dialogue even more complex. In the first place, because embryo research has been the subject of

debate for some time and consequently the discussion is organised and polarised. Various social groups and political parties in the Netherlands have already adopted clear positions on the subject. But also because the discussion about embryo research goes beyond research into technologies that can alter the DNA of embryos. Scientists would also like to create embryos for other purposes. For example fundamental research into early embryonic development to improve IVF procedures or to contribute to research into other reproductive techniques, such as *in vitro gametogenesis* (IVG, the transformation of cells, such as skin cells, into reproductive cells (Van Beers, 2018; Keulemans, 2018)).

The dialogue on nanotechnology illustrated that discussion of a technology with potentially broad implications not only raises new issues, but also familiar ones. For example, the dialogue on nanotechnology was not confined to the direct application of the technology, but also encompassed issues such as privacy, the ability to create the perfect human, the ethics of war and patents (Hanssen, Walhout & Van Est, 2008). In the discussion about germline genome editing, it is frequently asked what actions with human reproductive cells and embryos should be permitted and which should be prohibited. Because germline genome editing is closely connected with subjects such as scientific research with embryos, embryo selection, prenatal diagnosis and genetic screening, these related issues could also arise in the dialogue. It is important to clarify the relationships between these subjects, in science and in practice, and what needs to be discussed under each particular heading.⁵² That will ensure the dialogue remains comprehensible and manageable (Hanssen, Walhout & Van Est, 2008).

Different participants, different roles

The points made above mean that medical and scientific experts will have to play a *different* role in the dialogue, and that there will have to be input from *other* experts, as well as from various direct and indirect stakeholders (Jasanoff & Hurlbut, 2018; Van Est et al., 2017). With input from various experts with different backgrounds, the broad potential consequences for individuals, society and humanity can be discussed properly. One of the challenges in that context is the tendency for ethical and social issues to be phrased in terms of abstract concepts and principles, such as identity (in this case, genetic identity), human dignity and reproductive autonomy. In chapter 3, we showed that these concepts are not unambiguous and, consequently, it is not always clear what precisely is meant by the terms or how the terms relate to the possibility of using germline genome editing. In the dialogue, the terms must be clarified and explored: Why do people feel these concepts are important? What are the underlying values? And what conflicting arguments can be made based on the concepts and principles? Further examination of the underlying

52 Coinciding with the project 'National Dialogue on Human Genome Editing', the Ministry of Health, Welfare and Sport has commissioned a public dialogue on 'creating embryos specifically for research'. That dialogue will run from June 2019 until the end of May 2020.

values and considerations will also help to avoid a false consensus. For example, there is currently a broad agreement that using genome-editing technologies for germline genome editing is irresponsible and that applications for human enhancement are undesirable. However, as the preceding chapters have shown, that does not necessarily mean that there is agreement on *why* that is the case.

Combination of methods

To achieve the objective of the public dialogue, a mix of methods should be used. Public opinion research, for example with focus groups, interviews or surveys, provides insight into the attitudes and considerations of a small number of participants. But other activities and initiatives are needed to reach and inform a wider audience and persuade them to take part in a dialogue and form an opinion. For example, accessible sessions at events devoted to science would be one way of reaching a larger target group. Because the subject is so complex, it would also be worthwhile selecting a group of people who are actively engaged in the discussion and following them in the course of the public dialogue, for instance in the form of a citizens' panel. In this way, the dialogue could yield a variety of specific results that could make a valuable contribution to the political decision-making process.

Here we have described a number of the general ingredients that are needed for a public dialogue. The following section presents ten lessons for the *form* and *content* of a broad public dialogue on germline genome editing.

4.2 Lessons for the dialogue on germline genome editing

Section 4.1 showed that organising a successful public dialogue on germline genome editing entails various challenges, in terms of both its content and its form. Here we first discuss the lessons for the content and then the lessons for the form.

4.2.1 Lessons for the content of the dialogue

1. The questions of 'whether' and 'how' are interlinked – the dialogue should therefore not be limited to one or the other

Scientists and opinion makers regularly suggest that the discussion about the modification of the DNA of embryos, fertilised eggs or reproductive cells (and hence the modification of DNA of future persons) should not be concerned with the question of '*whether* we wish to use it', but only the question of '*how* we are going to use it'. The question of *how* we will use the technology is mainly concerned with

questions such as 'For what disorders will we use it?', 'How should we inform parents of the advantages and disadvantages and of the alternatives?' and 'How can we avoid a slippery slope towards human enhancement?'. This creates an apparent contradiction between discussing the *desirability* of germline genome editing and discussing the *conditions* under which it can be applied in practice. But research has shown that for the vast majority of people, the question of desirability and the conditions will be closely related. This means that the dialogue will certainly have to address the question of *whether* it is desirable to modify the DNA of future children. At the same time, that question cannot be answered without thinking about the purposes for which it will be used and the conditions under which it will be used.

2. Include the question of what is at stake in the dialogue

To expand the dialogue on human germline genome editing as widely as possible, it is important not to establish any prior constraints. In a democracy, there will always be differences of opinion about what is at stake with a subject like germline genome editing. For some, the key factor will be that it is a medical technology that can prevent the transmission of a serious heritable disorder, while others will focus on safeguarding fundamental values and principles.

The positions adopted on this subject are often implicit. An example of this is the sometimes expressed concern that genetic modifications are being made to future persons and generations, who are unable to give their consent. A counter-argument is the observation that no one is in a position to consent to his or her own genetic attributes. This type of argument is implicitly a normative assertion about what is or is not at stake, about what the discussion should or should not be about, and about the legitimacy of the arguments made in the discussion. The challenge is to expose this and to conduct a dialogue about whether, and if so why, such concerns (such as those relating to future generations) are relevant in the case of germline genome editing. In other words, any subject that participants in the dialogue regard as relevant must be acknowledged and explored in the dialogue.

3. Clearly explain what is needed to make use of human germline genome editing

Chapter 3 showed that the diversity and stratification of the discussion only becomes clear with an analysis of three domains: the domain of *research in the laboratory*, the domain of *research with people* and the domain of *application in practice*. The dialogue does not necessarily have to be structured in that way, but it must be clear to the participants what will be needed before genome-editing technologies can be used to modify the heritable DNA of embryos (and hence of future persons). For example, since its discovery in 2012 the CRISPR-Cas9 technology has been promoted as 'simple, inexpensive and accurate'. At the same time, scientists and ethicists agree that the technology is not yet safe and efficient

enough for clinical application. Consequently, they often call for prior preclinical research into its safety and efficiency. In other words, there is still considerable uncertainty about the opportunities for and risks of clinical application.

According to many scientists, the embryo research (with so-called 'residual embryos') that is permitted under the existing legislation is inadequate and research with embryos created specifically for the purpose is needed. Even this type of laboratory research with embryos is not yet capable of fully analysing the risks and possibilities of clinical applications. To learn more about these risks and possibilities, babies will have to be born from genetically modified embryos in an experimental setting, as in the case of the Chinese babies in 2018. Those babies (and their descendants) would, therefore, be taking part in an experiment.

Even if the technology is found to be sufficiently safe and effective for clinical application, various other factors will determine whether prospective parents can enjoy the benefits. Those factors include having prior knowledge of their genetic predisposition and the availability of sufficient and affordable reproductive clinics. How great the theoretical benefits of modifying heritable DNA will actually be in practice is, therefore, still uncertain; the same applies to who could profit from those benefits. That brings us to the following criterion.

4. Discuss the broader implications of targeted editing of the human genome for the individual, society and humanity

Technology is always used in a social context. The dialogue must, therefore, not only be about genome-editing technologies (such as CRISPR-Cas9) themselves (the purposes they can be used for, their medical benefits and their risks). Their impact on the practices and the social context in which they are applied must also be discussed. For example, there must be a discussion of how the practice of reproductive medicine and the norms and values surrounding pregnancy and reproduction will change. The same applies to attitudes towards sickness and disabilities. The accessibility of the technology for different persons and groups is another point that will need to be addressed.

5. Turn it around: think about the society of the future – what its core values should be and what role modification of heritable DNA in humans could play in that respect

Reflection on broad social consequences of germline genome editing also raises questions about the type of society we pursue and what key values should be protected in it. To foster discussion of these issues, it is important to avoid always taking the technology as the point of departure and then thinking about its impact on society. It can be fruitful to turn it around: by starting from the question of what

type of society we want, now and in the future, and then considering whether, and if so how, the modification of DNA of future persons can play a role in that. The scenarios and techno-moral vignettes in the second part of this report could help in this process.

4.2.2 Lessons for the form of the dialogue

6. Organise a dialogue not only between groups of stakeholders and interested parties, but also amongst themselves

Scientists, patients with a serious heritable disorder and prospective parents do not form a homogeneous group and their attitudes towards germline genome editing will differ. It is, therefore, important for these groups to converse not only with each other, but also amongst themselves. This can be organised in various ways, for example in focus groups or group dialogues, with scenario studies (see part 2), through interviews or with an Olympiad model.

7. Actively seek ways of reaching and informing less accessible groups and engaging them in the dialogue

It is not necessary for everyone to have an active voice in a dialogue, but the largest possible number of groups should be represented. Particularly groups that would be disinclined to engage in the discussion, that are difficult to reach or simply do not exist (think of future generations). This can be accomplished in various ways:

- Naturally, future generations cannot be consulted. However, they could be represented, for example by establishing a 'council of the future' to consider the issues from the perspective of future generations in the course of the dialogue.
- Young people and students could be involved through the participation of secondary schools, but also through sports clubs and social media.
- In the context of the public dialogue on the modification of heritable DNA, the Centre for Media and Health carried out a study of the media networks on the subject. The results of that study could be used to formulate a strategy for using social media and influencers to attract the attention of online groups (Lutkenhaus & Bouman, 2019).
- Magazines and the events they organise for their readers are a useful platform for informing members of the public and raising their attention to issues relating to reproduction, heredity and family.
- The use of non-traditional media or cultural events that reach a large and diverse audience, such as YouTube, vloggers and theatre plays or comedy, is worth considering.

- Look for good representatives of groups of stakeholders, such as representatives of groups of patients or people with a disorder.

8. A dialogue is not a platform for exchanging fixed views

There are various interests involved in this dialogue, such as the desire of many scientists to create embryos specifically for research and the desire of patients with a birth defect to avoid passing it on. Consequently, it might appear that positions have already been taken and that the purpose of the dialogue is to generate support for a particular viewpoint: whether or not the Embryo Act should be amended.

However, the crucial objective of the dialogue is to promote a joint process of opinion formation. It is a collective learning process. It must be clear in advance to the participants that they do not necessarily need to have made up their minds, that there is room to express doubts and reservations and to explore the issues together. As we stressed in lesson 1, the question of what is at stake is also not yet established. The values underlying the various intuitions, arguments and positions that have been adopted must, therefore, be constantly questioned during the activities in the dialogue. Figure 1 in the introduction of this report illustrated this process in diagrammatic form.

9. Involve and instruct appropriate experts and people with practical experience

The specialists and practical experts who are invited to take part in the dialogue must be clear about their role and must know what the central theme is and who their audience is. They must use language that is intelligible to everyone in attendance. A potential pitfall is that the presence of patients with a serious heritable disorder or 'learned' scientists might lead to certain themes being avoided or to people being too reticent to engage in the discussion.

In chapter 2, we concluded that the discussion in the Netherlands is currently dominated by experts. Many groups (including young people and people with a disability) and members of the public are scarcely involved. In section 4.1, we stressed the importance of providing all of the participants with sufficient information about the broad potential consequences for individuals, society and humanity to take part in the debate. That will call for a different approach than the experts are familiar with. They will, therefore, have to receive proper instruction on how to perform that role. It is also important to select appropriate specialists and practical experts carefully.

10. Think carefully about the themes, the material, terminology and the subject matter that will be discussed during a session

There are a number of points to consider regarding the information that has to be provided in the dialogue. They include the following:

- Present the material in a context that fits in with the personal environment of the participants. This could be done using the techno-moral vignettes (in the form of animations or some other suitable forms for discussing germline genome editing in a social context) based on the scenarios sketched in part 2 of this report. These vignettes are ideal for prompting reflection on the consequences for the personal environment of future persons, and the society in which they will live (see also criterion 3).
- It is not necessary for every social and ethical issue to be raised in every session of the dialogue. Nor is it feasible to discuss and reflect on every aspect in every session. The themes should be divided among different activities and geared to the envisaged audience. However, there should always be room for members of the audience to express their concerns and ask questions.
- Think carefully about the information that will be provided in advance. Promotional materials, introductions and questionnaires about attitudes towards the technology or germline genome editing could already influence or narrow the scope of the dialogue. For example, consider the possible impact if only technical information or only information about medical benefits and risks is provided. Combining medical and scientific information with information about the ethical issues and social consequences is an invitation for a broader dialogue.
- Medical terms such as ‘treatment, prevention, eradication’ of ‘disease’ must be used with caution in the dialogue.

4.3 Conclusion

In the early chapters of this report we described how a broad public dialogue should ideally reach and engage a wide audience. To reach an informed opinion diligently, the participants need to explore the possible consequences for the individual, society and humanity together. Such ethical and social issues encompass three domains: research in the laboratory, research with people and applications in practice. The issues can be clarified by providing insight into the various domains and – where desirable and possible – circumscribing the discussions within each of these domains. In each domain, issues arise at three levels: the instrumental, the social and the global (international). Naturally, some issues arise at all of the levels simultaneously.

The time dimension must also be taken into account in the discussions: the issues arise not only in the here and now, but also concern future generations and future societies. It is also important to bear in mind that the opinions of individuals towards the modification of human genetic material is dictated in part by their attitudes towards science and technology in general. Another important aspect is that there is disagreement, particularly among experts, about what the dialogue should be about: the development of new medical treatments that could prevent a lot of suffering, or the future, dignity, and identity of society and humanity. Closely interconnected with the dialogue on germline genome editing is the subject of creating embryos specifically for research. This combination of factors makes conducting a dialogue about modification of the heritable DNA of embryos a large and complex process. In this closing chapter of part I of the report, we have, therefore, provided guidelines for the content and the form of the dialogue in the shape of ten lessons. The techno-moral scenarios that we describe in the next chapter will also help in the process.

The broad public dialogue was launched on 9 October 2019 in Rotterdam. Various generations from various social groups will take part in the national dialogue. The complete agenda of meetings being organised as part of the dialogue can be found at www.dnadialoog.nl.

Part 2: Future scenarios

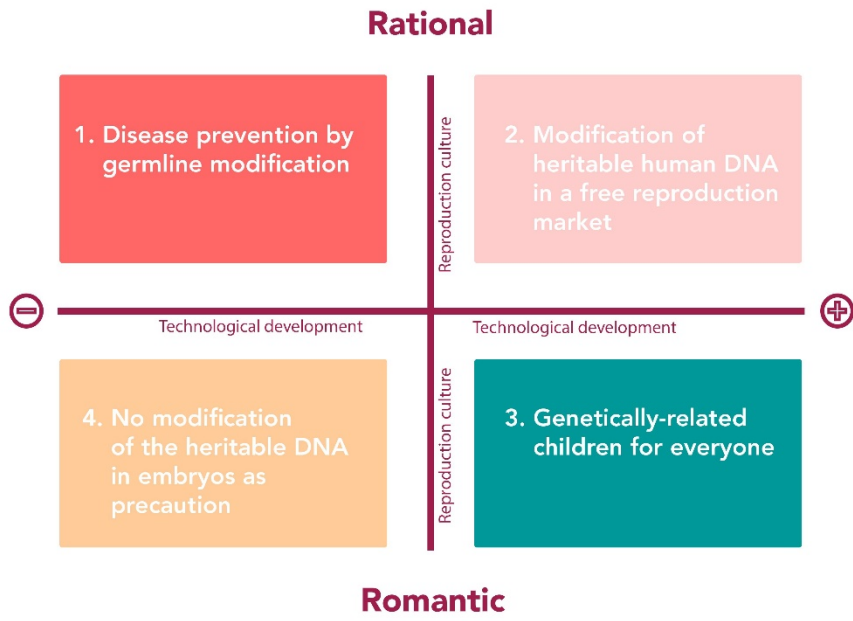
5 Future scenarios - the modification of heritable DNA

To specify and elucidate the possible consequences of germline genome editing for society and the individual, the Rathenau Institute has formulated four future scenarios. These scenarios provide guidelines for reflection on and discussion of the consequences during the broad public dialogue on human germline genome editing. They highlight moral and social dilemmas and value systems.

Scenarios are not predictions of the future. Accordingly, the aim of these scenarios is not to show what is *likely* to happen in the future, but to sketch various developments that *might* occur in the future. From these scenarios, NEMO Kennislink devised techno-moral vignettes: brief, interesting films that are set in the worlds described in the scenarios. The vignettes can be used, separately or in combination with the scenarios, to initiate discussion and stimulate opinion forming. They will catch the imagination and help the audience to put themselves in the place of the people who will live in these future worlds and will deal with the consequences of those scenarios.

To develop the scenarios, we conducted desk research and interviewed experts to identify trends and developments in the field of science and technology, national and international laws and regulations, the practice of pregnancy and reproduction, the economic organisation of science and reproductive medicine and relevant social developments. Most of the literature and the experts are the same as those consulted for part 1 (chapters 1 to 4) of this report. Based on this input, we distinguish two key variables: the pace at which science and technology relating to modification of heritable human DNA advances, and the cultural dimensions of reproduction and pregnancy. Set along two axes, this results in four distinct future scenarios, as can be seen in figure 3. A more detailed description of the methods we used to formulate these scenarios can be found in appendix 3 at the end of this report.

Figure 3: Key variables and description of scenarios



Source: Rathenau Institute

5.1 Four future scenarios

5.1.1 Scenario 1

The government stimulates the prevention of disease by making the modification of heritable human DNA accessible and common practice.

Introduction

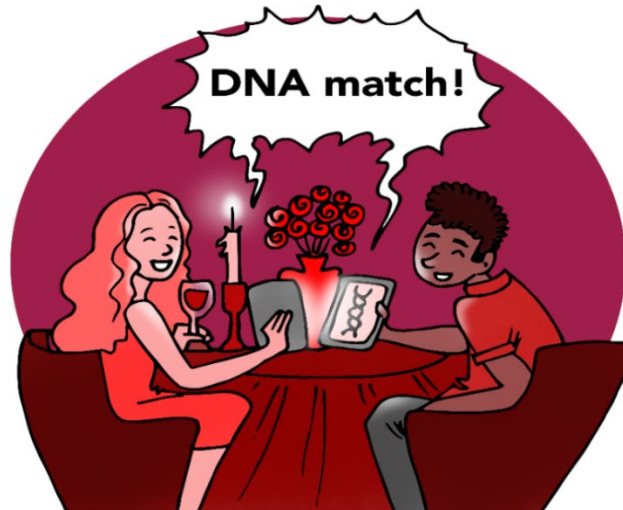
It is 2039. Disease prevention is high on the agenda of the Dutch healthcare system. The leading principle is cost-benefit analysis: the balance between the cost of *treating* diseases and the cost of *preventing* them. The social norm is that citizens take responsibility for their health and must do everything possible to avoid illness. Technology is actively used to register information about a person's health in their daily lives. In addition to wearable sensors that provide data such as heartbeat, blood pressure and exercise, there are also implants that measure blood sugar and hormone levels. People also have measuring equipment at home, for example an 'artificial nose' that analyses a person's breath to determine whether the lungs are working properly and sensors in the toilet bowl to provide data about bowel and liver function. Measured data are immediately analysed using artificial intelligence and users receive feedback so that they can take immediate action.



The surroundings have also been redesigned to help people make healthy choices: there are no longer any escalators in railway stations and most of the food sold there is healthy; at home, the refrigerator provides feedback about its contents, such as the sell-by date and the nutritional value of the products. Cars have disappeared from the street and have been replaced by vehicles propelled by a combination of muscle power and electricity.

The emphasis in the healthcare system is on primary care rather than hospital care. It is perfectly normal to visit GPs, dieticians, physiotherapists or mental coaches for regular consultations. These medical professionals help people to live a healthy life and monitor their condition as a sort of personal coach. People only go to hospital as a last resort and it is not seen as something to be proud of. It is expensive and a burden on society, and raises the question of whether you have been taking good care of yourself.

Genetic information plays an important role in the preventive programmes offered by health care professionals. People are happy to use this information. Everyone has a personal file containing their genetic profile, which is used to provide advice about dietary choices and exercise. The genetic profile also shows for which disorders you have an increased risk so that the risk can be constantly monitored. People who are carriers of a serious heritable disorder and who want a child can modify an embryo in an IVF procedure. Couples who want a child can also request a 'DNA match' between themselves and their partners. In that case, the two genetic profiles are used to predict the risk that their future children will have particular disorders. This information can be taken into account when entering into a relationship or in deciding whether to conceive.



How is modification of the heritable DNA in human embryos provided?

Prevention plays an important role in pregnancy and reproductive health. After all, the basis for a healthy life is already established during (or even before) pregnancy. Accordingly, an extensive national pregnancy and reproductive health programme has been established. Practically every couple that wants a child follows this programme, because they want to know that their child will be healthy and have the greatest possible chance of a long and healthy life. The range of screenings and treatments (before and after fertilisation) for future parents and their unborn child is consolidated in an extensive prevention programme. In addition to advice, sonograms and prenatal diagnosis, attention is also paid to the future child's health even before pregnancy. For example, prospective parents are offered an extensive programme devoted to nutrition, exercise and lifestyle aimed at ensuring a healthy pregnancy. In addition, the genetic profiles of both parents are analysed in order to establish whether there is an increased risk of passing on heritable disorders. Based on this analysis, they are given advice about various methods of conception. If there is an increased risk of a heritable disorder, they can then avoid passing it on to their offspring. Possible treatments are, for example, embryo selection, DNA modification or termination of the pregnancy, if anything goes wrong after conception. The recommendation for a particular treatment (embryo selection, genome editing or termination of the pregnancy) is based on a number of factors: the risk that the couple will have a child with a specific disorder, the seriousness of the disorder, the effectiveness of the various treatment methods and the balance between the benefits and the risks.

What preceded this situation?

In this scenario, the driving forces for developments in healthcare in general, and pregnancy and reproductive care in particular, were the desire to improve the *health* of adults and children and to increase the *cost-effectiveness* of the healthcare system. The national prevention agreement between the Dutch government, healthcare organisations, municipalities, educational institutions and industry concluded in 2018 had proved too non-committal. Eight years later (in 2026), alcohol consumption, smoking and obesity had not been reduced and the healthcare costs were still rising. In the meantime, the range of commercial health devices and tests had grown substantially. As a result, during this period the public had become more aware of their personal health and the risks to it. Consequently, it became easier and more natural for people to monitor and improve their health and to minimise risks to their health by changing their lifestyle. As a result, the government came under growing pressure from the public to facilitate such efforts.

In 2028, the World Health Organization (WHO) published a large and impactful study which once again confirmed the importance of lifestyle and early detection for public health and personal well-being. Because of the growing public support for prevention and the repeated demonstration of the extent of the health benefits, in that year the government decided to rigorously take on prevention and launched a large-scale national prevention programme. One aspect of this programme was investment in advanced portable devices with which data about physical functions and health could easily be measured, collected and shared. With the help of algorithms, these data could be automatically analysed. Medical dossiers were already entirely digital; the additional data that individuals could now collect themselves provided valuable insights.

Meanwhile, the science and technology of making genetic changes in reproductive cells or a recently fertilised egg improved, although there were no major breakthroughs. In 2020, a group of scientists in the UK published a paper describing the study in which, for the first time, they had repaired the gene that causes Huntington's disease in the laboratory with CRISPR-Cas9, using embryos and without creating a pregnancy. In the ensuing years, there were many publications about the successful application of genome-editing technologies in human embryos. Various technological obstacles had been resolved in relation to genetic screening, the chance of success of IVF treatment and the targeted modification of heritable human DNA without causing unintended effects.

In 2026, the first clinical trials started in the US and the first *genetically modified babies* (since Lulu and Nana in China) were born with a repaired Huntington's gene. When the initial results seemed positive – the babies were healthy, grew normally and DNA research had shown that no unintended modifications had been

made – the demand for the use of such technologies also increased in the Netherlands. A growing number of prospective parents who were carriers of a serious heritable disorder asked their doctor for treatments to ensure that they would not pass on that disorder – and the predisposition to it – to their child. Associations representing patients urged the government to allow the modification of heritable traits in embryos for certain disorders.

On the basis of a cost-benefit analysis, in some cases the modification of DNA was found to be a more cost-effective method of preventing heritable disorders than embryo selection. In 2030, it was, therefore, decided to legally allow germline genome editing of human embryos, and a child to be born from them, in those cases. An additional benefit was felt to be that passing on the status of carrier of a recessive genetic disorder can be prevented with *genetic modification*, whereas with embryo selection, choosing an embryo that is a carrier of a recessive gene is sometimes inevitable. In that case, the child that grows from the embryo is not ill, but could pass the disease on to any children if his or her partner is also a carrier of that recessive gene. Because the efficiency and safety is different for every genetic disorder – depending on the genetic defect that causes the disease – a committee of experts drew up a list of the disorders for which *genome editing* was the preferred method and the disorders for which embryo selection was more appropriate. The committee monitored compliance with the rules. Because the technology gradually improved after 2030, the list of disorders was regularly evaluated and disorders were added to the list. The committee is currently evaluating what gains could be made in terms of health benefits and cost effectiveness if *genome editing* could be used in embryos in cases where the disease cannot be prevented, but the risk of having it could be reduced. Since the introduction of the possibility of treating the heritable DNA of embryos, a large database has also been maintained with information of persons whose genome has been edited. Based on the database, cohort studies were carried out into the effects, including unexpected and unintended effects, of genome editing. This database can later be used to provide counselling to genetically modified persons who want to have children.

Why do prospective parents use germline genome editing in embryos?

No one is obliged to participate in the preventive programme or to use the treatments and coaching that are available. Nevertheless, almost everyone chooses to use at least some of the available services. It has become the social norm. In a society where prevention is important, parents feel a great sense of responsibility to have a healthy child. Good parenthood is associated with the idea that care for your child begins before pregnancy. Medical advice and protocols are strongly geared to promoting the health of the unborn or not yet conceived child. Prospective parents who choose not to follow them are generally criticised in the

GP's consulting room and by friends and family, for example. Doctors and prospective parents increasingly feel responsible for the health of future children and are, therefore, afraid of being criticised if a child is born with a disorder that could have been prevented before fertilisation, pregnancy or birth. Or of being held responsible for the fact that their child is a carrier of a heritable disorder and could, therefore, possibly have a sick child later.

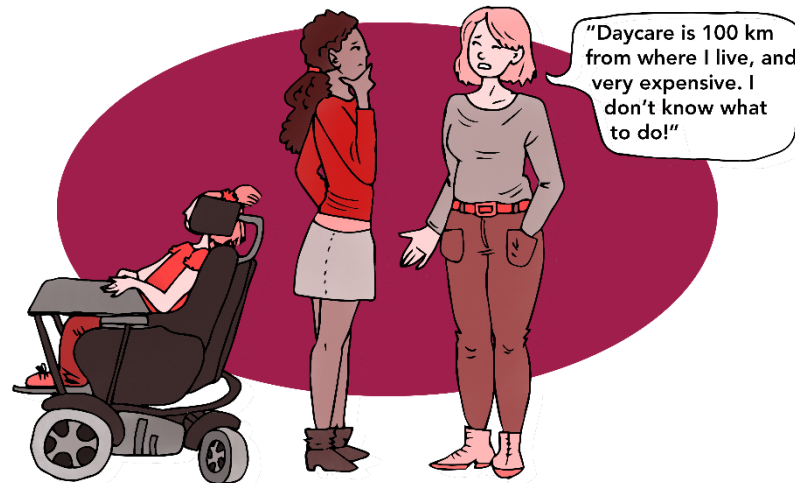
What is the government's role?

The government facilitates, stimulates and finances the use of germline genome editing if it is appropriate for achieving the goal of preventing serious heritable disorders. On the other hand, reimbursement of the costs of treatment and care for persons with a disorder has become more moderate. Because these disorders are less common, the market invests less in developing more effective treatments for them. A consequence of the preventive policy is that some patients feel that living with their disease makes them inferior and that they are an unwanted expense for society.

Dilemmas:

- The societal focus on prevention yields health benefits and prevents a lot of suffering caused by disease, but also leads to a heavy medicalisation of many aspects of life, such as reproduction and pregnancy. Children whose genome was edited will be monitored after their birth.
- Screening and treatment options are offered based on a free choice. Prospective parents can use them if they wish and do not have to pay for them. This seems to increase their freedom of choice: there are more options and access to them does not depend on a person's financial situation. However, the government and society send a strong message by making screening, IVF and genome-editing technologies with which DNA of a future child can be modified available. There is also a consciously greater emphasis on prevention than on treatment or care. Because participation in the programme is the norm, and the prevailing opinion is that preventing is better than curing, there is social pressure to choose screening and/or treatment. The question, therefore, is whether prospective parents actually have the freedom *not* to choose it.
- Emphasising preventing over curing diseases is very beneficial for society in financial terms. For individuals, it could actually have a negative effect, for example if parents personally have to pay the costs of caring for children who, despite everything, are not born entirely free of disorders. Or if couples have to undergo screening, IVF treatment and embryo selection or modification of the embryo's DNA with every pregnancy because one of the couple is a carrier of a disease and there is a slight risk of it being transmitted. This is stressful, while there is no certainty that the treatment will be a success.

- If there are fewer people with a disease or handicap, the care for and the costs of the disease or handicap will decline. But it also reduces the visibility of people with diseases and disabilities in society. That can lead to fewer facilities for these people or to stigmatisation and loss of solidarity. That will not reduce the suffering of people who do have a disorder or handicap.



- A rational cost-benefit analysis seems to provide clear criteria for deciding on the cases in which modification of heritable DNA of human embryos should or should not be permitted. But if the technology improves or the situation changes, the analysis will change. The assessment or analysis has to be made repeatedly and there can be no 'once and for all' agreement on which cases are acceptable and which are not.
At the same time, a cost-benefit analysis could produce a different outcome than the assessment made by an individual, a doctor or the public.

5.1.2 Scenario 2

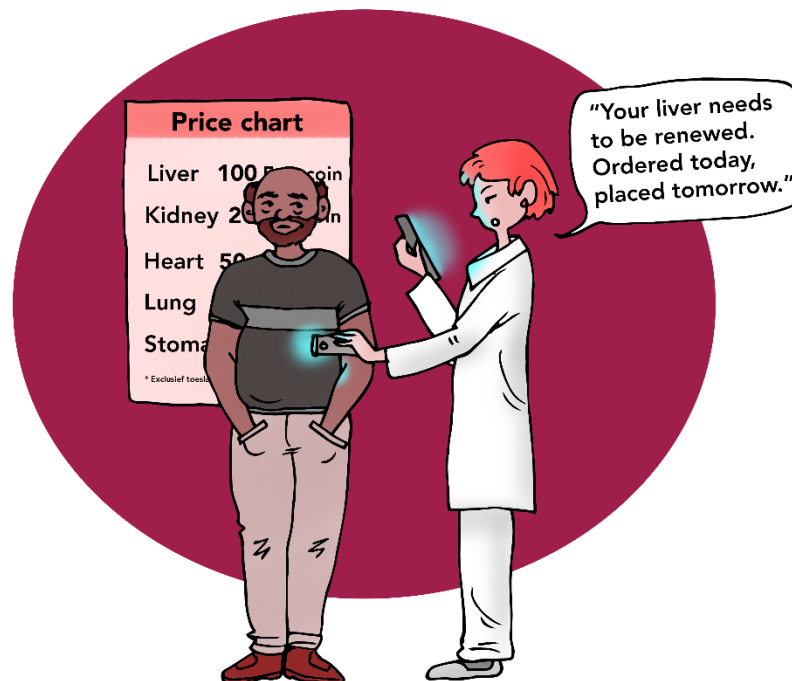
Modification of heritable human DNA in a free reproduction market

Introduction

It is 2039. Self-determination is high on the agenda in the healthcare sector in the Netherlands and Europe. Individuals have considerable freedom to choose a specific treatment, doctor or clinic. Treatments whose effectiveness have been scientifically proven are offered in regular hospitals. Treatments that have not been proved effective, but for which there is a demand, are offered in specialised private

clinics, which distinguish themselves not only with the treatments they offer, but also with their extra service. For those who can afford it, there is more luxury, such as a private room, gourmet meals and private nurses. Consequently, there is a wide range of treatments available throughout Europe that Dutch citizens can avail of.

A lot is possible in the field of medical technology. For example, organs or other bodily materials that are genetically similar to the body's can be cultivated 'on demand'. They are grown in pigs or produced with a 3D printer. The composition and dosage of medication are generally tailored precisely to the individual, with the help of personal organs-on-a-chip with which the effect of different medicines can be tested. With the combination of advanced medical imaging technologies and artificial intelligence, the composition of tissue can be examined without having to take samples of blood or bodily materials. Certain disorders can, therefore, be diagnosed very accurately and at an early stage. The availability of these technologies often depends on an individual's financial situation. The more individualised a diagnosis, the more expensive it is.



Work, school and day-to-day life are dominated by competition. And data are constantly being collected about what a person is doing, and how. Since 2025, the smartphone has gradually disappeared. With developments in the field of smartwatches, augmented reality glasses and smart contact lenses, you no longer

need a device in your pocket to connect with the world of telecommunication and entertainment or to share your experiences and successes with others. The technology is becoming increasingly intimate: our physical and mental activities are constantly registered. These data, in combination with your social media history, play an important role in job interviews and assessments. Perfection is the norm. From birth, a child's development must be optimal because dips in their school performance could later affect them in a job search or reduce their chances of being admitted to the best schools and universities. Accordingly, parents closely monitor their child's development from birth. There is now a huge market for technical applications and services that promise to enhance children's development. Instead of an old-fashioned cot, most parents nowadays have a 'think inside the box': a box fitted with sensors, software and interactive holograms designed to optimise the baby's mental and physical development. Parents who can afford it seek extra counselling and coaching for their children, such as a 'programming for infants' course.

This desire for perfection has also reached the medical world: there is a demand not only for treatments against diseases, but also for treatments designed to enhance certain traits and abilities. For example, brain implants that can improve a person's concentration and memory, or gene therapy that increases a person's stamina. People want to use this type of treatment to increase their chance of getting a good education or job.

The pursuit of perfection, the technological progress and the importance of self-determination is also reflected in reproductive healthcare. Reproduction is seen as a means of having offspring with the desired traits. This is a matter for the individual, where prospective parents have considerable freedom of choice: in principle, their wishes must be respected and facilitated. With new genome-editing technologies, the heritable DNA of human embryos can be modified simultaneously in various places. Thanks to the rapid development of artificial intelligence (AI), big data analysis and knowledge of genetics, it is easier to understand and predict the effects of modifications (or combinations of modifications) of the DNA. As a result, multi-factorial characteristics can also be influenced. All in all, prospective parents have a great many technological options available to them to manage the process of becoming pregnant, procreating and raising their future child as they wish.

What preceded this situation?

As with many other medical technologies, human genome-editing technologies have really taken off. The Chinese babies Lulu and Nana, who were the first genetically modified children when they were born in November 2018, proved to be perfectly healthy, excelled at school and are now studying at prestigious universities. In the five years after they were born, and a temporary worldwide ban

was declared on the modification of heritable characteristics of future children, scientists did not stand still. In the United Kingdom, for example, experiments started with human embryos, without leading to the birth of babies. By the time the temporary ban was lifted, the technology had advanced to such an extent that many scientists and physicians regarded it as safe enough to experiment with trial subjects. Consequently, in 2025 a child was born in whose DNA the mutation that normally causes cystic fibrosis had been repaired. Since then, technologies that can prevent the transmission of genetic disorders have been seen as promising medical treatments. The United States, the United Kingdom, China and South Korea were the first countries to amend their legislation to allow clinical applications with embryos. Most other countries followed suit, including a number of European countries.

The Netherlands initially remained cautious, but that changed as the international acclaim for the experiments with genome editing to modify heritable human DNA increased. In 2022, Jennifer Doudna and Emmanuelle Charpentier won the Nobel Prize in Chemistry for the development of CRISPR-Cas9. In 2032, the research group that successfully repaired the cystic fibrosis gene in the DNA of a future child for the first time won the Nobel Prize for Medicine.

Parallel to the rapid growth in the use of genome-editing technology to modify the heritable DNA in human embryos, the use of predictive genetics also expanded substantially. AI and *big data analysis* had made it easier to understand and predict the effects of modifying (combinations of) genes. As a result, it was possible to prevent not only serious heritable disorders, but also 'polygenic' disorders (where multiple genes are modified simultaneously) and influence multi-factorial characteristics such as intelligence, physical features, empathy or athleticism.

The EU decided that the internal market, which guarantees free movement of goods, persons, services and capital, should also apply to healthcare. To that end, a European Health Area was created in 2032 and European citizens had access to health services throughout Europe. This generated wider competition in the field of healthcare and medical treatment and created room for private medical platforms, also in the Netherlands.

How is modification of the heritable DNA in human embryos provided?

By 2039, healthcare has been internationalised and privatised. Private clinics offer various treatments with which different genes can be modified simultaneously, for example to minimise the risk of disorders with a partially genetic cause (such as dementia, autism, diabetes and obesity). These clinics also offer treatments to improve traits: standard packages for 'musicality', 'athleticism', 'learning performance' or 'leadership qualities' for example, but also 'bespoke' treatments

geared to the specific needs and wishes of clients. The scientific underpinning of these treatments is often dubious and many scientists warn that such human traits are too complex to be influenced with genome editing. Nevertheless, the range of treatments and the turnover of these clinics has grown, partly because they invest heavily in marketing. In addition, clinics and companies often also fund research into the effectiveness and safety of the treatments they provide.



Why do prospective parents use germline genome editing in embryos?

Parents are free to modify the heritable traits of their future child and have a large degree of freedom in choosing the characteristics they do or do not want their child to have. The desire for perfection is a factor in the parents' choice. They want the best for their child, but they also want 'the best child'. Parents are willing to make sacrifices to give their child the best possible chance in life, for example even temporarily incurring debt to do so. All in all, a vibrant industry has grown in this field, in which demand and supply drive one another. There is a wide range of possibilities, and choices are heavily influenced by fads and/or subcultures. Like other reproductive technologies, technologies to modify heritable DNA and the accompanying treatments for parents, such as IVF and genetic screening, are

readily available to everyone. However, they have to be paid for. In reality, enhancement applications are, therefore, mainly available to the wealthy. This threatens to create a new class of 'genetically modified children'. These are often children from well-off families who have been given an extra, genetic advantage. The differences are often already noticeable in the crèche and in kindergarten classes: children whose genetic predisposition to intelligence has been improved perform better on average than their non-genetically modified peers. At the same time, some experts argue that the better scores of those children are not the result of their increased intelligence and that there are other explanations for the discrepancies. Parents who invest time and money in genetically improving their children's intelligence often also devote time and money to improving their cognitive skills in other ways, for example through cramming or courses. These parents will probably also send their children for regular *health checks*.

When the genetically modified children reach the age when they themselves are thinking of procreation, they will perhaps also consider modifications to give their child the desired traits and so increase their opportunities. However, there is always the risk that in addition to desired traits, DNA modification could have unintended side effects.

What is the government's role?

With the introduction of the European Health Area, private multinational IVF clinics can also open in the Netherlands. With these private clinics, the range of treatments provided in the Netherlands increases and enhancement applications also become available. Supply and demand drive one another and the range of applications steadily expands.

Modifying embryos is seen as a personal decision in which the final say rests mainly with prospective parents. The wishes of parents can differ and must be respected and facilitated. The government only reimburses treatment of serious heritable disorders, but encourages the development and availability of new technologies through the free market. The range of treatments for parents and children is, therefore, largely controlled by private clinics, which are run by large, multinational companies. The government regulates them, but is hampered by the difficulty of acquiring reliable scientific information about the effectiveness and safety of the various treatments for modifying the heritable DNA in embryos. Parents therefore also bear personal responsibility for the success of the treatment. They can insure themselves against the risk of something going wrong and continually have their children screened for negative effects in order to prevent that.

**Dilemmas:**

- Making applications of genome-editing technologies to modify DNA in embryos available through private clinics increases the supply and, hence, the reproductive autonomy of prospective parents. But these possibilities are mainly available to people who can afford them. This will reinforce inequality because the (claimed) genetic advantage will be in addition to the socioeconomic advantage these children already have.
- Surrendering the supply of reproductive and human enhancement treatments to commercial businesses threatens the safety and transparency of the medical treatments. Mistakes and a lack of reliable scientific evidence can be disguised. The government, therefore, has little grip on the quality of the care and it is difficult for physicians and care providers to estimate the value of a treatment. Consequently, the possibility of providing follow-up for parents, children and their children through screening for any unintended and negative effects is also lost.

- The freedom of parents to use reproductive technologies can also encroach on the freedom of children by inhibiting their freedom to shape their lives. Children are, in a way, reduced to a product of their parents' wishes. At the same time, enhancement treatments could actually increase children's freedom by giving them greater possibilities and options for personal development.
- In this scenario, the desire for perfection is a driving force behind the development and availability of technology. However, this urge for perfection has implications for parent-child relationships, relationships between children, solidarity with people who are ill and *non-gene-edited* children and their parents, as well as for the children of gene-edited children.
- If prospective parents are free to choose the traits they wish to give to their child, it increases their reproductive autonomy. However, they could all choose the same traits, with a decline in biological and social variation as a result. We would, therefore, be creating uniformity.
- In this scenario, a great deal is permitted and possible in the Netherlands, but only after international research shows that the treatments are safe and effective. This seems sensible, but could also lead to a form of 'moral free riding' or 'ethics dumping'. Risky and ethically controversial research is not permitted in this country, but we do profit from the results of research in countries where it is allowed. These are often countries with less strict rules and a less prosperous population.

5.1.3 Scenario 3

Genetically-related children for everyone

Introduction

It is 2039. *Equality* and *self-fulfilment* are important driving forces in the Netherlands. The prevailing notion is that people must be able to develop their talents, competences and interests as best as possible. A widely-held idea is that everyone has a natural affinity with particular activities, such as sport, playing music, writing, crafting, caring or coaching. People's well-being is greatest if they have the chance to blossom by doing something that comes naturally to them. From a young age, children are encouraged to discover and develop their natural abilities and talents. They are, therefore, introduced to various activities to test their aptitude from a very young age. Their aptitude is also investigated with genetic tests and personality tests.

In this scenario, illness is seen as physical or mental dysfunction which disrupts the natural balance between the individual's preferences, talents and physical abilities. Disease is usually a physical problem, but how a person experiences illness and

the influence it has on his or her well-being depends on the extent to which it impairs their capacity to shape their life and personal development. To remedy this disrupted capacity, the available treatments and support are mainly concerned with what a person wants or has to do to continue developing his or her talents. The best treatment or assistance for a particular individual has to be determined in each case and is impossible to capture and standardise in medical guidelines. Care is, therefore, highly personalised. Physicians often speak at length with their patients about how they experience their disease or disability and are assisted in this by social workers. They also have advanced technology at their disposal.

People with a physical disability are fitted with customised prostheses, which are operated directly via a connection to (still functioning) nerves and muscles. Technologies inside and on the surface of the body support the integration of body and prosthesis. Many serious diseases of the blood and immune system can be remedied with the help of gene therapy. By modifying the DNA in the cells (such as blood stem cells) of existing persons, diseases cannot affect those cells. These modifications are not made in heritable DNA and are, therefore, not passed on to the patient's children. Personal *biomarkers* and genetics are used intensively to match medication to the wishes and biological traits of individual patients.

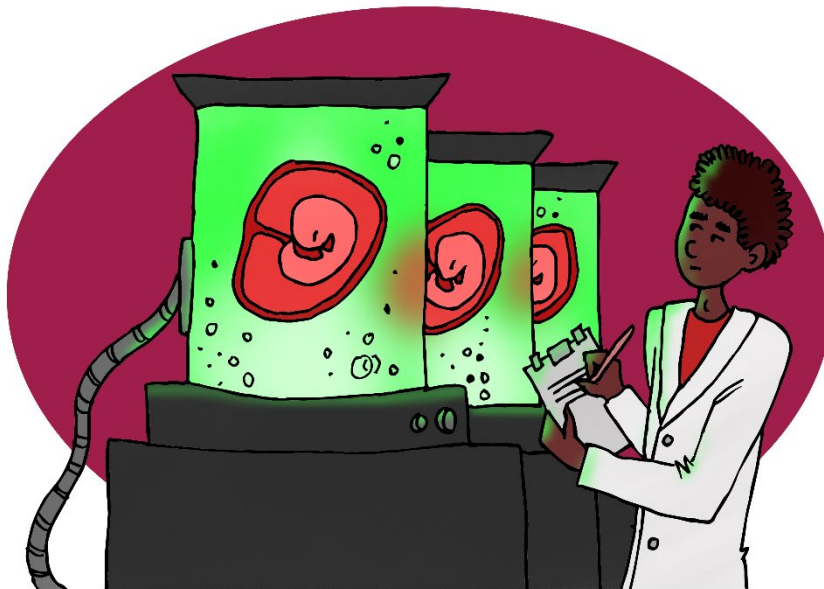
Having genetically related children is seen as a special event in the natural course of a person's life, one that everybody who wants it should have the opportunity to experience. This also includes people who are infertile and same-sex couples. This principle is the driving force behind the development and availability of reproductive technologies. Examples of such technologies are artificial wombs or *In Vitro Gametogenesis*, a technology by which reproductive cells, egg cells or sperm cells are produced from skin cells. When these cells are fertilised, they can produce embryos from which a genetically related child can grow.

How is modification of the heritable DNA in human embryos provided?

As with other reproductive procedures, treatments involving the modification of the heritable DNA in human embryos are only available in the regular healthcare system in the Netherlands. In every case, the prospective parents, the treating physician and an independent physician arrive at a joint decision on whether the modification of the heritable DNA of the future child fits in with the prospective parents' aims and wishes. The framework that is used for making that decision can lead to a different result in each individual case. The treatments are not only available to prospective parents with a serious heritable disorder, but also for couples with an increased chance of disorders such as autism and depression, or conditions such as high blood pressure, a high cholesterol level or diabetes. Many prospective parents do not see such genes as part of a person's identity, but rather as an unnatural 'intruder' that actually constrains a person's identity. Prospective

parents who feel that such a condition or disorder will hamper their child's self-fulfilment might consider modifying their future child's heritable material. The same applies to physical features that do not match the prevailing 'norm', since abnormal features could hamper the child's development and equal opportunities.

The Netherlands has remained an 'island' in terms of reproductive health: in contrast to many other countries, reproductive medicine is not available in private clinics. It is, therefore, not possible to go to private clinics for reproductive treatments that are not available in regular healthcare in the Netherlands, while people in other countries can.



What preceded this situation?

In the 2020s, various malpractices came to light in relation to adoption and surrogacy. Consequently, innovative forms of artificial reproduction increasingly came to be considered as a reasonable alternative to the 'natural method'. By 2028, it was no longer unusual for reproductive cells to be created in the lab or for an artificial womb to be used. These are just two of the many instruments used to increase the chance of success of IVF, to reduce the physical strain for women and to enable couples to have genetically related children. As a result, a growing number of women have completed an IVF trajectory.

When the use of genome-editing technologies to modify heritable traits in an embryo was permitted in 2028, the large number of couples that used IVF and other

artificial reproductive technologies were pioneers. For them, choosing to make permanent genetic changes in their embryos, that were already created in the laboratory with IVF, was a relatively small step. These children appeared to do well after birth and as they grew up: they seemed to have a naturally balanced character and to possess many distinct capacities and talents to help in their self-fulfilment. Because the efficiency of IVF had meanwhile improved and the procedure had become less burdensome for women, a growing number of couples that did not immediately need it chose to become pregnant with the help of an IVF programme so that they could also permanently alter the DNA of their child (and all of his or her children).

Genome-editing technologies developed rapidly, so there are now a number of accurate technologies available to permanently modify heritable DNA without any unintended negative side-effects. Multifactorial traits can also be influenced. Until well beyond 2020, only the prevention of serious heritable disorders was permitted in the Netherlands, but the range of applications was expanded in 2029. With the use of these technologies, children can all start life on an equal footing and have the possibility of developing themselves in accordance with their natural aptitudes.

Why do prospective parents use germline genome editing in embryos?

Parents use germline genome editing treatments to give their child a good start in life. Their ideas of what constitutes a 'good life,' and what that entails for their children, vary. Many parents already know a lot about their genetic predisposition and, therefore, have a good impression of what talents they could pass on to their children, but also what impediments there could be. Accordingly, even before a pregnancy they think about the best way (fitting in with their personal situation) of addressing these impediments. They can also turn to various medical professionals for advice. For example, they consider the pros and cons of preventing disease by modifying the DNA in the embryo and the accompanying follow-up for the child and all of his or her descendants. One alternative could be medication, in combination with therapy or support once the child is born.

What is the government's role?

An important driving force for the government is equality. That includes *reproductive equality*: everyone should be able to have their own genetically related children. It also means endeavouring to ensure that every future child has the chance to make the most of his or her talents and capabilities. Sometimes, it is necessary to give nature a helping hand by creating the desired genetic traits. The government provides a lot of treatments and conducts publicity campaigns targeted at people who could benefit from them. It also verifies the safety and effectiveness of the available treatments by monitoring for any unforeseen or unintended side-effects.. The government also facilitates equal access to the treatments and provides

counselling for families and for the modified children when they themselves have children.



Dilemmas:

- In this scenario, genome-editing technologies are used to modify heritable traits based on an ideal of equality rather than competition. The impact depends greatly on how people use them. If parents have a large degree of freedom, there is a chance that they will choose for DNA modifications that will give their children and grandchildren a competitive advantage over other children. Or it could become fashionable to choose specific modifications. If the government retains total control, the situation comes close to eugenics: there is a chance that preference will be given to traits that are valuable to society. What will then happen with people with traits that are not directly regarded as valuable? Or if particular physical features are associated with social status?
- Some traits are seen as an impediment to establishing a personal identity, while other traits are seen as part of that identity. To what extent is a physical handicap or a physical feature part of a person's identity? What is the situation with a disorder like autism? Many of these traits are regarded not only as

'disorders' by people who have them, but also as part of who they are. They actually owe their unique way of thinking or unique view of the world, or their particularly well-developed traits such as creativity or stamina, to their 'disorder'.

- A 'good genetic basis' gives everyone a good start in life. That can reduce inequality. But it also increases one's personal responsibility to keep up and make a success of their life. After all, you have been given every opportunity to do so. It is, therefore, your own fault if you can't make a success of your life.
- Equality based on genetics could be desirable from the perspective of society. However, it is not clear what function genetic variation has at the level of the population. Do we face a risk, in evolutionary or biological terms, if we aim for genetic equality? And what if unintended modifications are introduced in DNA that have undesirable or harmful effects? How can they be prevented from spreading through the population? Who is responsible if a treatment goes wrong?
- The assumption in this scenario is that the choice on whether or not to use genome-editing technologies is a joint decision by the parents and physicians, and is based on different types of information. But is everyone really capable of making a well-considered choice? If everyone is capable of understanding the available information and making a choice based on it, the decision is based on what is good for the unborn baby, the parents and society. If some people are unable to make such well-considered choices, it could create inequality based on the capacity to understand complex information.

5.1.4 Scenario 4

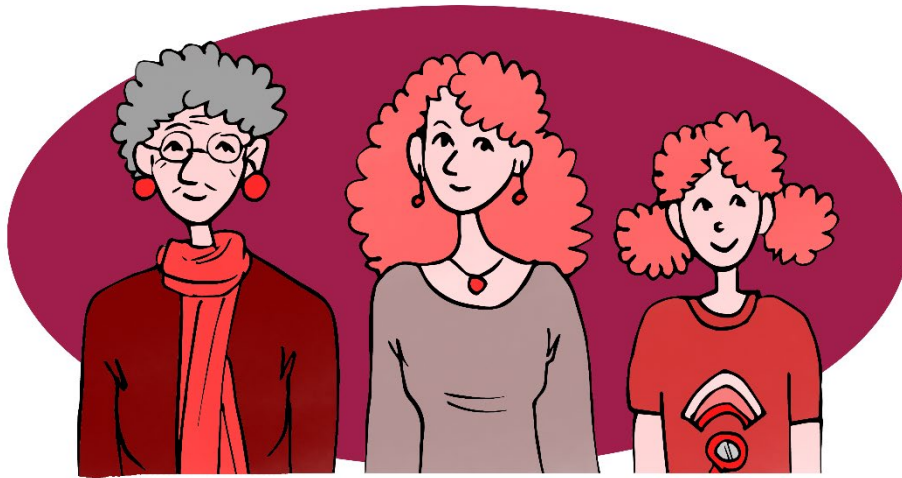
No modification of the heritable DNA in embryos as a precautionary measure

Introduction

It is 2039. In the Netherlands, fundamental principles determine whether new medical technologies will be permitted in the healthcare system, and for individuals, whether they will use them. Some key principles in these considerations are *precaution*, *human dignity* and *protection of life*. 'Does this fit in with how we want to live' is a more important question than 'what will we gain from it?'. For example, health care professionals discuss the emotional and psychological consequences of an intervention or diagnostic test at length with the patient. What does it mean to have detailed information about your own genes, or about your children's genes? How do people experience living with a donor organ? Is it similar to or different from living with artificial implants? And is it different in the case of an implant in their hip rather than their brain?

Considerations of this type do not mean that people will not want to use medical technology. A treatment often enables a person to shape his or her life the way they want it to be. However, these considerations mean that people will not automatically avail of a treatment, a diagnostic technique or a medical technology, and a lot of attention is devoted to their potential negative effects.

Fundamental principles also play a role in the regulation of biomedical research. One is that risks must be excluded as far as possible for participants in clinical and pre-clinical research. If necessary, every possible measure must be taken to reverse any negative consequences. In the laboratory, the acceptability of treatments is also guided by fundamental principles. Respect for the natural integrity of life, animals and humans largely determines what experiments will or will not be carried out on cell material or tissue. Especially when it comes to embryonic tissue or reproductive cells, scientists are very reluctant to conduct experiments. Creating human embryos specifically for research is not permitted, because this could undermine the protection of early life.



In this scenario, the modification of the genome of future children is not permitted in the Netherlands. This is the result of a deliberation based on fundamental principles: it is contrary to the right of children to an open future or a breach of human dignity and it harms the unique identity of children. Another important factor in this consideration is the precautionary principle: the consequences of using genome-editing technologies for the individual and for the population in general cannot be properly estimated in advance. If a child who is born from a genetically modified embryo has health complaints, it is impossible to establish whether they are an unintended effect of the use of genome-editing technologies. The risks are, therefore, regarded as uncertain and unacceptable, especially because the

consequences can be passed on from one generation to the next and are irreversible.

What preceded this situation?

A public dialogue in 2019 revealed that the general public in the Netherlands were ambiguous about the use of human embryos for scientific research. Most Dutch people recognised the benefits of such research, but they were uncertain about the moral status of an embryo. Is it in principle the start of a new life and, therefore, worthy of protection, or 'merely' a clump of cells? As a result of this outcome, amendment of the Embryo Act was delayed. It was, therefore, not possible to create embryos specifically for research into IVF technologies and genome editing. In 2024, the new Minister of Health, Welfare and Sport encountered a lot of opposition to a proposal to amend the law.

Various events and incidents relating to genome editing prompted discussion of the safety of these technologies. In 2025, for example, it was announced that the first genetically modified babies, which had been born in China, had serious health complaints and repeatedly had to spend lengthy periods in hospital. These complaints might have been the result of side-effects from the genetic modification. In the same year, a large, international consortium published a study showing that genome-editing technologies to modify heritable human DNA often caused unintended DNA modifications. Because it was not possible to predict where these unintended changes would occur in the DNA, the seriousness of the consequences could not be foreseen. Accordingly, in 2026, in the Netherlands it was decided to maintain not only the ban on creating embryos, but also the total ban on making changes in the DNA of offspring.

In the late 2020s, there were major developments in the genetic modification of embryos in other countries, such as Sweden, the United Kingdom and the United States. A lot of research was carried out in these countries. Clinical trials led to the birth of dozens of healthy babies from embryos in which the gene for serious diseases such as cystic fibrosis or Tay-Sachs disease (a hereditary metabolic disease) had been repaired. After their birth, the children's health was closely monitored. Around 2030, these success stories revived the discussion concerning the genetic modification of human embryos to prevent the transmission of genetic disorders. Prospective parents with an increased risk of passing on a heritable disorder felt that they were being denied access to a potential treatment.

In 2031, however, a genetically modified child died of leukaemia in the United States at the age of four. Her parents brought a legal action against the IVF clinic that had carried out the genetic modification (the gene for cystic fibrosis had been repaired in the girl). They lost the case. Although it was possible in theory, they

could not show that the disease was an (unintended) consequence of the modification of the child's heritable DNA. In the Netherlands, the argumentation was reversed. Since the possibility that the modification of the heritable DNA had caused the leukaemia could not be ruled out, the incident was seen as confirmation that the statutory ban on modifying heritable DNA was correct – the reason being that the ban actually protected future children and generations from serious risks.

How is modification of the heritable DNA in human embryos provided?

In this scenario, the modification of the DNA in a human embryo is not permitted – either in the laboratory or in practice. Prospective parents with a serious, heritable disorder who would like to have their own genetically related child can prevent transmission of the disorder using embryo selection. They can also consider donation of a reproductive cell (an egg or semen) or adoption.

Couples that want to make use of other treatment options, and that have enough money, can go abroad. Prospective parents can go to Belgium and the United Kingdom, where the modification of the DNA in embryos can be used to prevent serious, heritable disorders. In the United States, it is also possible to select desired traits such as creativity, athleticism and musicality. Eastern and Southern European countries also permit more in terms of preventing or reducing the risk of heritable disorders such as autism and breast cancer. The treatments in other countries are not always successful, which leads to a discussion of how we in the Netherlands should deal with children who were conceived in another country and might have been genetically modified. Should the care that is needed if medical complications arise in these children be reimbursed under the health insurance? Or should the costs be borne by the parents who chose to use these prohibited treatments? Some people are also concerned that the treatments in other countries could cause undesirable, harmful genetic mutations to spread through the Dutch population. Unfortunately, there is no test to show whether a child has been genetically modified.

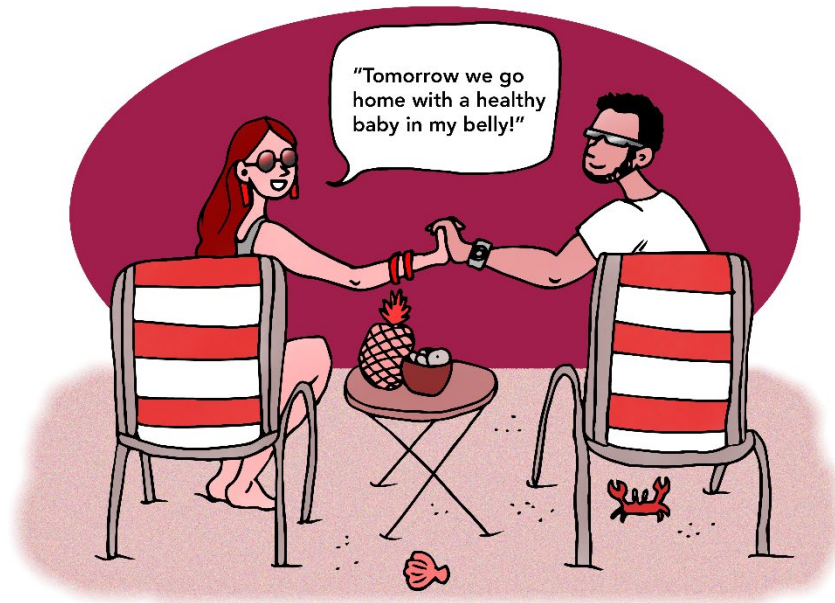


A number of sub-cultures have arisen around the subject of reproduction in the Netherlands. For example, there are do-it-yourself (DIY) biotechnology communities that experiment with genetic technologies, and sometimes also with genetic modification of their children. These experiments are conducted outside the regular healthcare system and it seems almost impossible to monitor such communities in practice.

Dilemmas:

- Further development of genome-editing technologies for the modification of heritable human DNA will ultimately require research with embryos that have been created specifically for the purpose. Creating embryos for research creates possibilities for scientific research and experiments, but conflicts with broadly supported principles such as the protection of early life.
- The introduction of genome-editing technologies to modify the DNA of future children is accompanied by various risks. Unintended changes in the DNA could perhaps have negative consequences that will affect genetically modified babies for the rest of their lives. Attempting to exclude this type of risk could be an obstacle to introducing new technologies that could prevent a lot of suffering. The suffering that could be prevented by the intended effects, therefore, has to be weighed up against the suffering that the unintended effects could cause, also in future generations.
- In this scenario, the precautionary principle plays an important role in the assessment of the acceptability of risks in the Netherlands. There are, therefore, fewer possible treatments in the Netherlands than in some other

countries. Prospective parents could choose to use technologies in other countries that are not permitted in the Netherlands ('germline tourism').



This has a number of possible consequences:

- a. The quality of the treatments and the counselling cannot be verified. Parents might make a choice that they later regret or might choose a treatment that does not benefit the future child (or his or her children).
- b. In the Netherlands, the money that is spent on developing and providing treatments to modify heritable DNA in embryos could be spent on providing alternative treatments and good care for patients who are born with a disorder.

Bibliography – Part I

Allenby, B. & D. Sarewitz (2011). *The Techno-human Condition*. Boston: MIT press.

Baalen, S. van & J. Gouman (2019). 'Erfelijk DNA veranderen: dialoog over de grenzen'. Website Rathenau Instituut, 24 juni 2019.

Baalen, S. van, J. Gouman & P. Verhoef (2019). *Wezenlijk anders. Lessen voor de maatschappelijke dialoog over het combineren van menselijk en dierlijk celmateriaal*. Den Haag: Rathenau Instituut.

Beers, B. van, (2019). 'Welkom in de CRISPR-dierentuin. Juridische grenzen aan genetische modificatie van het nageslacht in het CRISPR-tijdperk.' *Nederlands Juristenblad*, 24, pp. 1722- 1730.

Beers, B. van, 'We zijn blij met de assemblage van onze iZoon. In: *De Groene Amsterdammer* 8 februari 2018a.
www.groene.nl/artikel/we-zijn-blij-met-de-assemblage-van-onze-izoon

Beers, B. van, 'Waar ligt de grens tussen genezen en verbeteren?'. In: *NRC Handelsblad* 10 december 2018b.
www.nrc.nl/nieuws/2018/12/07/waar-ligt-de-grens-tussen-genezen-en-verbeteren-a3059906

Blendon, R., M. Gorksi & J. Benson (2016). 'The public and the gene-editing revolution'. *NEJM* 374, nr. 14, pp. 1406-1411.

Bodegom, L. van, & I. Vos, 'Het debat over verbetering van onze genen is veel te pragmatisch'. In: *Nederlands Dagblad* 26 september 2017.
www.nd.nl/nieuws/opinie/het-debat-over-verbetering-van-onze-genen-is-veel.2801493.lynkx

Boon, A., 'Knutselen aan genen roept vragen op'. In: *Reformatoisch Dagblad* 30 april 2016.
www.rd.nl/vandaag/buitenland/knutselen-aan-genen-roept-vragen-op-1.542997

Cleene, D. de (2017). 'Vlaming verwacht (te) veel van DNA'. In: *EOS wetenschap* 25 november 2017.
www.eoswetenschap.eu/gezondheid/vlaming-verwacht-te-veel-van-dna
zie ook: www.demaakbaremens.org/themas/genetica/denkt-vlaming-genen-en-dna

Critchley, C. et al. (2019). 'Predicting public attitudes toward gene editing of germlines: the impact of moral and hereditary concern in human and animal applications. *Frontiers in Genetics* 9, pp. 1-14.

COGEM (2016). *Gentechdebat op scherp: invalshoeken voor een vruchtbare dialoog*. Bilthoven: COGEM.

COGEM & Gezondheidsraad (2017). *Ingrijpen in het DNA van de mens. Morele en maatschappelijke implicaties van kiembaanmodificatie*. Bilthoven: COGEM.

COGEM (2019a). *Update signalering 'ingrijpen in het DNA van de mens'*. Bilthoven: COGEM.

COGEM (2019b). *Percepties van burgers over genetische modificatie. Een kwalitatieve en kwantitatieve verkenning*. Bilthoven: COGEM.

Committee on Science, Technology, and Law; Policy and Global Affairs; National Academies of Sciences, Engineering, and Medicine & Olson S (red.) (2016). *International Summit on Human Gene Editing: A Global Discussion*. Washington, DC: The National Academies Press.

Cong, L. et al., (2013). 'Multiplex genome Engineering Using CRISPR/Cas Systems'. *Science* 339, nr. 6121, pp. 819-823.

Council of Europe (1997a). Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine. Convention on Human Rights and Biomedicine.
rm.coe.int/168007cf98

Council of Europe (1997b). Explanatory Report to the Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine. Convention on Human Rights and Biomedicine.
rm.coe.int/16800ccde511n

Cornel, M., M. Smalbrugge & R. Haselberg, 'Denk na over de preventie van erfelijke ziekten via DNA'. In: *Trouw*, 20 januari 2019.
www.trouw.nl/opinie/denk-na-over-de-preventie-van-erfelijke-ziekten-via-dna~be3743de/

Danish Council on Ethics (2016). *Statement from the Danish Council on Ethics on Genetic Modification of Future Humans. In Response to Advances in the CRISPR Technology*. Copenhagen: Danish Council on Ethics.

www.etiskraad.dk/~media/Etisk-Raad/en/Publications/Statement-on-genetic-modification-of-future-humans-2016.pdf

David Cyranoski (2019). 'What's next for CRISPR babies?'. *Nature* 566, pp. 440-442.

Dijk, D. van & E. van Hoek-Burgerhart (2019). 'Wie wij zijn: de waarde van embryo's in het kiembaandebat'. *Podium voor Bioethiek* 26, nr. 1, pp. 17-20.

Dijk, D. van & S. Luitwieler (2019) 'Tijd voor bewustwording, bezinning en dialoog over embryothematiek'. *Lindeblad* 16, nr. 1, pp. 1-2.

Engels, J. 'Waarom sleutelen aan het DNA van embryo's volgens deze voortplantingsarts straks misschien heel gewoon is'. In: *Trouw* 15 december 2018. www.trouw.nl/nieuws/waarom-sleutelen-aan-het-dna-van-embryo-s-volgens-deze-voortplantingsarts-straks-misschien-heel-gewoon-is~b0fcaedf/

Embryowet (2002, 20 juni). Geraadpleegd op 11 maart 2019, van wetten.overheid.nl/BWBR0013797/2018-08-01

Est, R. van et al., (2014). *Intieme technologie: de slag om ons lichaam en gedrag*. Den Haag: Rathenau Instituut.

Est, R. van & A. van Waes m.m.v. A. de Vries (2016). *Elf lessen voor een goede Energiedialoog*. Den Haag: Rathenau Instituut.

Est, R. van et al. (2017). *Regels voor het digitale mensenpark. 'Telen' en 'temmen' van de mens via kiembaanmodificatie en persuasieve technologie*. Den Haag: Rathenau Instituut.

European Group on Ethics in Science and New Technologies (2016). *Statement on Gene Editing*.

ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_statement.pdf

Europese Unie (2000). *Handvest van de Grondrechten van de Europese Unie*. 18 december 2000, 2000/C 364/01.

www.europarl.europa.eu/charter/pdf/text_nl.pdf

Fransen, R., 'Embryo's zijn te repareren'. In *Nederlands Dagblad* 3 augustus 2017. www.nd.nl/nieuws/wetenschap/embryo-s-zijn-te-repareren.2754718.lynkx

Geesink, I., 'Kweekembryo-debat raakt aan het leven van toekomstige generaties'. In: *Trouw* 19 april 2017. www.trouw.nl/nieuws/kweekembryo-debat-raakt-aan-het-leven-van-toekomstige-generaties~b06bac8c/

German Ethics Council (2017). *Germline Intervention in the Human Embryo. German Ethics Council calls for Global Political Debate and International Regulation*. Berlijn: German Ethics Council. www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/englisch/recommendation-germline-intervention-in-the-human-embryo.pdf

German Ethics Council (2019). *Intervening in the Human Germline. Executive Summary & Recommendations*. Berlijn: German Ethics Council. www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/englisch/opinion-intervening-in-the-human-germline-summary.pdf

Gils, S. van, 'Crispr: vragen rond het wondermiddel voor de 'betere mens''. In: *Het Financieele Dagblad* 7 april 2018. fd.nl/morgen/1248322/crispr-vragen-rond-het-wondermiddel-voor-de-betere-mens

Gils, S. van, 'Designbaby op komst?'. In: *Het Financieele Dagblad* 19 januari 2019. fd.nl/futures/1285708/designbaby-op-komst#

Gyngell, C., T. Douglas, & J. Savulescu. (2017). 'The Ethics of Germline Gene Editing'. *Journal of Applied Philosophy* 34, pp. 498-513.

Habets, M., L. van Hove & R. van Est (2019). *Genome editing bij planten en gewassen. Naar een modern biotechnologiebeleid met oog voor verschil in risico's en bredere afwegingen*. Den Haag: Rathenau Instituut

Hanssen, L., B. Walhout & R. van Est (red.) (2008). *Tien lessen voor een nanodialoog. Stand van het debat rondom nanotechnologie*. Den Haag: Rathenau Instituut.

Hendriks, S. et al. (2018). 'Reasons for being in favour of or against genome modification: a survey of the Dutch general public'. *Human Reproduction Open*, pp. 1-12.

Herzberger, R., 'Deze stap had nooit gezet mogen worden'. In: *NRC Handelsblad* 1 december 2018.

www.nrc.nl/nieuws/2018/12/01/deze-stap-had-nooit-gezet-mogen-woorden-a2878635

Houten, M. van, 'Ziektes genezen, daar was Jezus Christus toch ook al mee bezig?'. In: *Trouw* 15 maart 2019.

www.trouw.nl/religie-filosofie/ziektes-genezen-daar-was-jezus-christus-toch-ook-al-mee-bezig~b1719182/

IBC (2015). *Report of the IBC on Updating its Reflection on the Human Genome and Human Rights*. Parijs: UNESCO International Bioethics Committee.

Jackson, D., R. Symons & P. Berg (1972). 'Biochemical method for inserting new genetic information into DNA of simian virus 40: circular SV40 DNA molecules containing lambda phage genes and the galactose operon of Escherichia Coli. *Proceedings of the National Academies of Sciences* 69, nr. 10, pp. 2901-2909.

Jasanoff, S. (2019). *Can Science make Sense of Life?* Cambridge: Polity Press.

Jasanoff, S. and B. Hurlbut (2018). 'A global observatory for gene editing'. *Nature* 555, pp. 435-437.

Jasanoff, S., B. Hurlbut, & K. Saha (2015). 'CRISPR democracy: gene editing and the need for inclusive deliberation'. *Issues in Science and Technology* 32, pp. 25-32.

Kamerstukken II 2000/2001, 27 423, nr. 3.

Kamerstukken II 2016/2017, 29323, nr. 110.

Kamerstukken II 2017/2018, 34 990, nr. 1.

Keulen, I. van & R. van Est 'Wat is de mens? Over (biomedische) technologie en mensverbetering'. Website Rathenau Instituut, 17 april 2018.

www.rathenau.nl/nl/maakbare-levens/wat-de-mens-over-biomedische-technologie-en-mensverbetering

Keulemans, M., 'Is de supermens in aantocht?' In: *De Volkskrant* 18 april 2015.

www.volkskrant.nl/wetenschap/is-de-supermens-in-aantocht~bf678e83/

Keulemans, M., 'De voortplanting gaat radicaal veranderen' In: *De Volkskrant* 9 juni 2018.

www.volkskrant.nl/wetenschap/de-voortplanting-gaat-radicaal-veranderen~b176bf81/

Koninklijke Nederlandse Akademie van Wetenschappen (2016). *Genome Editing, Visiedocument KNAW*. Amsterdam: KNAW.

Koelewijn, J. & F. Weeda, "'Ik vind het veranderen van DNA niet doodeng", In: *NRC Next* 5 januari 2019.

www.nrc.nl/nieuws/2019/01/04/ik-vind-het-veranderen-van-dna-niet-doodeng-a3127924

Kundina, O & P.P. Verbeek (2019). 'Ethics from Within: Google Glass, the Collingridge Dilemma, and the Mediated Value of Privacy'. *Science, Technology & Human values* 44, nr. 2, pp. 291-314.

Lander, E. et al. (2019). 'Adopt a moratorium on heritable genome editing'. *Nature* 567, pp. 165-168.

Ledford, H. (2015). 'The Landscape for Human Genome Editing'. *Nature* 526, pp. 310-311.

Ledford, H. (2016). 'Bitter fight over CRISPR patent heats up'. *Nature News* 529 p. 265.

Lente, V. van der (2016) 'Uitslag publieksonderzoek: zo denken wij over genmodificatie'. Website De Kennis van Nu, 27 april 2016.
dekennisvannu.nl/site/artikel/Uitslag-publieksonderzoek-zo-denken-wij-over-genmodificatie/8132

Liang, P. et al. (2015). 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes'. *Protein & Cell* 6, nr.5, pp. 363-372.

Lutkenhaus, R. & M. Bouman (2019). *De medianetwerken rond kiembaanmodificatie*. Gouda: Centrum Media & Gezondheid.

Ma, H. et al. (2017). 'Correction of a pathogenic gene mutation in human embryos'. *Nature* 548, pp. 413-419.

Mali, P. et al. (2013). 'RNA-Guided Human Genome Engineering via Cas9'. *Science* 339, nr. 6121, pp. 823-826.

Mastenbroek, S. & S. Repping, 'Laat het verbod op embryokweek los'. In: *NRC Handelsblad*, 4 december 2018.

www.nrc.nl/nieuws/2018/12/03/laat-het-verbod-op-embryokweek-los-a3009216

Maxmen, A. & D. Mallet (2015). 'Three technologies that changed genetics'. In: *Nature* 528, pp. S2-S3.

Mil, A. van, H. Hopkins & S. Kinsella (2017). *Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the royal society*. London: Hopkins van Mil.

Molder, H. te (2016). 'Reflectie: maatschappelijke discussies over gentechnologie: een kijkje achter de coulissen.' In: Mampuys, R. & F. van der Wilk (red). *Gentechdebat op scherp. Invalshoeken voor een vruchtbare dialoog*. Bilthoven: COGEM, pp. 16-18.

Molteni, M (2018) 'Now you can sequence your whole genome for just \$200'. In: *WIRED*, 19 november 2018.

www.wired.com/story/whole-genome-sequencing-cost-200-dollars

Mulder, F. 'Schaft onze soort zichzelf af?'. In: *De Groene Amsterdammer* 16 mei 2018.

www.groene.nl/artikel/wie-alles-doorziet-ziet-niets

National Academies of Sciences, Engineering, and Medicine (2017). *Human Genome Editing. Science, Ethics, and Governance*. Washington D.C.: National Academies Press.

National Academies of Sciences, Engineering, and Medicine (2019) 'Second International Summit on Human Genome Editing: Continuing the Global Discussion'. Website The National Academies Press, Januari 2019.

Nuffield Council on Bioethics (2016). *Genome Editing. An Ethical Review*. Londen: Nuffield Council on Bioethics.

<http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf>

Nuffield Council on Bioethicis (2018). *Genome Editing and Human Reproduction. Social and Ethical Issues*. Londen: Nuffield Council on Bioethics.

<http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf>

Pessers, D., 'De Grensvervaging tussen mensen beter maken en betere mensen maken'. In: *De Groene Amsterdammer* 6 september 2017.
www.groene.nl/artikel/de-aanbidding-van-het-dna

Raad van State (2016). *Nader rapport inzake het voorstel van wet, houdende wijziging van de Embryowet*. Den Haag: Raad van State.

Regalado, A., 'Exclusive: Chinese Scientists are Creating CRISPR Babies' In: *MIT Technology Review* 25 november 2018.
www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/

Rek, W, de., 'En de mens schiep de mens'. In: *De Volkskrant* 15 oktober 2016.
www.volkskrant.nl/wetenschap/de-mensheid-perfectioneren-moeten-we-dat-willen~b9bb4c27

Rerimassie, V. & D. Stemerding (2012). *Politiek over leven. In debat over synthetische biologie*. Den Haag: Rathenau Instituut.

Rijksoverheid (2017). *Vertrouwen in de toekomst. Regeerakkoord 2017-2021*.
www.rijksoverheid.nl/regering/documenten/publicaties/2017/10/10/regeerakkoord-2017-vertrouwen-in-de-toekomst

Savulescu, J. & N. Bostrom (red.) (2009). *Human enhancement*. Oxford: Oxford University Press.

Santen, G. & F. Hes, 'Eerst dialoog over modificatie embryo's'. In: *Trouw* 14 januari 2019.

Seldenrijk, R., 'Liever puur natuur dan de uiterste perfectie van designbaby's'. In: *Reformatisch Dagblad* 10 januari 2019.
www.rd.nl/opinie/liever-puur-natuur-dan-de-uiterste-perfectie-van-designbaby-s-1.1539790

Sluys, K. 'No Milk Today. Meningen over biotechnologie in ons land.' Website VPRO, 28 november 2002.
www.vpro.nl/programmas/tegenlicht/lees/bijlagen/2002-2003/de-gemiste-kans/no-milk-today.html

Smink M., et al. (2017). *Samen kennis aanboren. Verkenning van kennis en opvattingen over ultradiepe geothermie*. Den Haag, Rathenau Instituut.

Stelling, T. 'Kinderwens? Laat je niet gek maken door de ivf-industrie'. In: *De Correspondent* 19 september 2018.

decorrespondent.nl/8702/kinderwens-laait-je-niet-gek-maken-door-de-ivf-industrie/511145333468-3ba9b09e

Swierstra, T. (2009). *Willen we alles wat? Ethische controversen rondom wetenschap en technologie ontrafeld*. Den Haag: ZonMw.

Travis, J. (2015). 'Making the cut. CRISPR genome-editing technology shows its power.' *Science* 350, nr. 6267, pp. 1456-1457.

UNESCO (1997). *Universal Declaration on the Human Genome and Human Rights*. www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights

Verordening (EU) 536/2014 van het Europese parlement en de raad van 16 april 2014 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik en tot intrekking van Richtlijn 2001/20/EG.

<http://data.europa.eu/eli/reg/2014/536/oj>

Verhoef, P. (2018). 'Los het tekort aan eicellen niet op met schimmige handel'. *Podium voor Bioethiek* 25, nr. 3, pp. 6-9.

Vries, A. de, A. et al. (2015) *Bouwstenen voor participatie*. Den Haag: Rathenau Instituut.

Wert, G. de, 'Ziekten uitbannen moet kunnen'. In: *NRC Handelsblad* 22 oktober 2016.

www.nrc.nl/nieuws/2016/10/21/ziekten-uitbannen-moet-kunnen-4856226-a1527865

Wert, G. de & W. Dondorp, 'Denk aan de zieken voordat je begint over designer babies' In: *NRC Handelsblad* 5 februari 2016.

www.nrc.nl/nieuws/2016/02/05/denk-aan-de-zieken-voordat-je-begint-over-designer-1584900-a98713

Wert, G. de & W. Dondorp, 'Voor oprukkende gentechniek zijn strenge regels nodig'. In: *NRC Handelsblad* 18 december 2018.

www.nrc.nl/nieuws/2018/12/17/voor-oprukkende-gentechniek-zijn-strenge-regels-nodig-a3060958

Wouters, M. & V. Rerimassie (2017). *De Burger aan het Woord: publieksopvattingen over moderne biotechnologie*. Capelle aan den IJssel: InSites Consulting.

List of newspaper articles consulted

Alderliest, A. & T. Boer, 'Behoud verbod op embryokweek'. In: *Trouw* 25 juni 2018.

Beers, B. van, 'Designbaby of de voortplanting van de toekomst'. In: *De Groene Amsterdammer* 8 februari 2018.

Beers, B. van, 'Waar ligt de grens tussen genezen en verbeteren?'. In: *NRC Handelsblad* 10 december 2018.
www.nrc.nl/nieuws/2018/12/07/waar-ligt-de-grens-tussen-genezen-en-verbeteren-a3059906

Bodegom, L. van & I. Vos, 'Ons DNA vraagt om moreel debat'. In: *Nederlands Dagblad* 26 september 2017.

Boon, A. 'Knutselen aan genen roept vragen op'. In: *Reformatorisch Dagblad* 30 april 2016.
www.rd.nl/vandaag/buitenland/knutselen-aan-genen-roept-vragen-op-1.542997

Cornel, M., M. Smalbrugge & R. Haselberg, 'Denk na over de preventie van erfelijke ziekten via DNA'. In: *Trouw* 20 januari 2019.
www.trouw.nl/opinie/denk-na-over-de-preventie-van-erfelijke-ziekten-via-dna~be3743de/

Ditmars, A. van, 'Sleutelen aan de natuur? Als er niemand door lijdt, is het geen probleem' (Interview met Bas Haring & Marli Huijjer). In: *Trouw* 17 mei 2018.
www.trouw.nl/religie-filosofie/sleutelen-aan-de-natuur-als-er-niemand-door-lijdt-is-het-geen-probleem~b38846b5c/

Engels, J. 'Wat nu wordt verguisd, is straks geaccepteerd' (Interview met Sjoerd Repping). In: *Trouw* 15 december 2018.

Fransen, R. 'Herschrijven genen vraagt om breed debat'. In: *Nederlands Dagblad* 8 september 2016.
www.nd.nl/nieuws/wetenschap/herschrijven-genen-vraagt-om-breed-debat.2070247.lynkx

Geesink, I. 'Kweekembryo-debat raakt aan het leven van toekomstige generaties'. In: *Trouw* 19 april 2017.

www.trouw.nl/nieuws/kweekembryo-debat-raakt-aan-het-leven-van-toekomstige-generaties~b06bac8c/

Gils, S. van 'Crispr: Vragen rond het wondermiddel voor 'betere mens'. In: *Het Financieele Dagblad* 7 april 2018.

fd.nl/morgen/1248322/crispr-vragen-rond-het-wondermiddel-voor-de-betere-mens

Gils, S. van, 'Designbaby op komst?'. In: *Het Financieele Dagblad* 19 januari 2019.

fd.nl/futures/1285708/designbaby-op-komst#

Gunst, J. 'NPV kies eigen toon in debat gentechniek'. In: *Reformatorisch Dagblad* 8 maart 2019.

www.rd.nl/vandaag/binnenland/npv-kiest-eigen-toon-in-debat-gentechniek-1.1552003

Herzberger, R. 'Deze stap had nooit gezet mogen worden'. In: *NRC Handelsblad* 1 december 2018.

www.nrc.nl/nieuws/2018/12/01/deze-stap-had-nooit-gezet-mogen-woorden-a2878635

Houten, M. van, 'Ziektes genezen, dat wilde Jezus toch ook al?' (Interview met Martina Cornel en Matthias Smalbrugge). In: *Trouw* 15 maart 2019.

www.trouw.nl/religie-filosofie/ziektes-genezen-daar-was-jezus-christus-toch-ook-al-mee-bezig~b1719182/

Keulemans, M. 'Is de supermens in aantocht?'. In: *de Volkskrant* 18 april 2015.

www.volkskrant.nl/wetenschap/is-de-supermens-in-aantocht~bf678e83/

Keulemans, M. 'De genetische revolutie is begonnen'. In: *de Volkskrant* 24 december 2015.

www.volkskrant.nl/nieuws-achtergrond/de-genetische-revolutie-is-begonnen~b0476b14/

Keulemans, M. 'De voortplanting gaat radicaal veranderen'. In: *de Volkskrant* 9 juni 2018.

www.volkskrant.nl/wetenschap/de-voortplanting-gaat-radicaal-veranderen~b176bf81/

Keulemans, M. 'Eigenzinnige Chinees maakte nog een genbaby – en wordt vervolgd'. In: *de Volkskrant* 21 januari 2019.

www.volkskrant.nl/nieuws-achtergrond/eigenzinnige-chinees-maakte-nog-een-genbaby-en-wordt-vervolgd~b562f64b/

Koelewijn, J. & F. Weeda, 'Ik vind het veranderen van DNA niet doodeng' (Interview met Sjoerd Repping). In: *NRC.next* 5 januari 2019.

www.nrc.nval/nieuws/2019/01/04/ik-vind-het-veranderen-van-dna-niet-doodeng-a3127924

Köhler, W. 'Knip, plak, crispr en.....de bruine ogen zijn blauw'. In: *NRC.next* 01 oktober 2016.

www.nrc.nl/nieuws/2016/09/30/knip-plak-crispr-en-bruine-ogen-zijn-blauw-4538594-a1524213

Mastenbroek, S. & S. Repping, 'Laat het verbod op embryokweek los'. In: *NRC Handelsblad* 4 december 2018.

www.nrc.nl/nieuws/2018/12/03/laat-het-verbod-op-embryokweek-los-a3009216

Mulder, F. 'Schaft onze soort zichzelf af?'. In: *De Groene Amsterdammer* 16 mei 2018.

www.groene.nl/artikel/wie-alles-doorziet-ziet-niets

'Een nieuwe techniek maakt het genetisch aanpassen van levende wezens, inclusief de mens, sneller en goedkoper'. In: *Nederlands Dagblad* 1 december 2015.

'Embryo's zijn te repareren'. In: *Nederlands Dagblad* 3 augustus 2017.

'Geen moratorium op onderzoek naar genbaby's'. In: *NRC handelsblad* 11 december 2015.

www.nrc.nl/nieuws/2015/12/11/geen-moratorium-op-onderzoek-naar-genbabys-1569160-a254461

Pessers, D. 'De Grensvervaging tussen mensen beter maken en betere mensen maken'. In: *De Groene Amsterdammer* 6 september 2017.

www.groene.nl/artikel/de-aanbidding-van-het-dna

Ramaker, R. 'Gentechexperiment met verbeterde baby is roekeloos'. In: *Elsevier weekblad* 5 december 2018.

www.elsevierweekblad.nl/opinie/opinie/2018/12/verbeterde-baby-156313w/

'Riskant geknutsel'. In: *Reformatorisch Dagblad* 29 maart 2017.

Rek, W. de, 'En de mens schiep de mens' (Interview met Annelien Bredenoord). In: *de Volkskrant* 15 oktober 2016.

www.volkskrant.nl/wetenschap/de-mensheid-perfectioneren-moeten-we-dat-willen~b9bb4c27/

Santen, G. & F. Hes 'Eerst dialoog over modificatie embryo's'. In: *Trouw*, 14 januari 2019

Seldenrijk, R. 'Liever puur natuur dan de uiterste perfectie van designbaby's'. In: *Reformatorisch Dagblad* 10 januari 2019.

www.rd.nl/opinie/liever-puur-natuur-dan-de-uiteerste-perfectie-van-designbaby-s-1.1539790

Stelling, T. 'Een eikel uit een huidcel: vruchtbaarheid voor iedereen is nabij'. In: *De Correspondent* 17 februari 2017.

decorrespondent.nl/6222/een-eikel-uit-een-huidcel-vruchtbaarheid-voor-iedereen-is-nabij/365473025148-0720239a

Stelling, T. 'Kinderwens? Laat je niet gek maken door de ivf-industrie'. In: *De Correspondent* 19 september 2018.

decorrespondent.nl/8702/kinderwens-laat-je-niet-gek-maken-door-de-ivf-industrie/511145333468-3ba9b09e

Vaessen, T. 'D66 maakt de weg vrij voor industriële fabricage baby's' (Interview met Britta van Beers). In: *Het Financieele Dagblad* 23 december 2017.

fd.nl/weekend/1229975/d66-maakt-weg-vrij-voor-industriële-fabricage-van-baby-s

Voormolen, S. 'Genetisch experiment embryo's toegestaan'. In: *NRC Handelsblad* 2 februari 2016.

www.nrc.nl/nieuws/2016/02/02/genetisch-experiment-embryos-toegestaan-1584323-a1316923

Voormolen, S. 'Erfelijke DNA-fout gerepareerd in menselijk embryo'. In: *NRC Handelsblad* 3 augustus 2017.

www.nrc.nl/nieuws/2017/08/02/erfelijke-dna-fout-gerepareerd-in-menselijk-embryo-12342289-a1568719

Voormolen, S. 'Genetici denken al aan klinische embryotests'. In: *NRC Handelsblad* 4 augustus 2017.

Voormolen, S. & C. Berthelot, 'Geboren in de babyfabriek- de techniek is bijna zover'. In: *NRC Handelsblad* 27 januari 2018.

www.nrc.nl/nieuws/2018/01/26/geboren-in-de-babyfabriek-a1589934

Voormolen, S. 'Waarom greep niemand in bij de crispr-baby's?'. In: *NRC Handelsblad* 9 maart 2019.

www.nrc.nl/nieuws/2019/03/08/babies-born-waarom-greep-niemand-in-a3952575

Wassink, J. 'Behoedzaam voorwaarts met CRISPR-Cas'. In: *De Groene Amsterdammer* 16 mei 2018.

www.groene.nl/artikel/de-evolutie-in-eigen-hand

Weeda, F. 'Wie wil er nou geen kind met goede genen?' (Interview met Marcel Zuijderland). In: *NRC Handelsblad* 29 januari 2018.

www.nrc.nl/nieuws/2018/01/26/wie-wil-er-nou-geen-kind-met-goede-genen-a1589957

Wert, G. de & W. Dondorp, 'Denk aan de zieken voordat je begint over designer babies' In: *NRC Handelsblad* 5 februari 2016.

www.nrc.nl/nieuws/2016/02/05/denk-aan-de-zieken-voordat-je-begint-over-designer-1584900-a98713

Wert, G. de, 'Ziekten uitbannen moet kunnen'. In: *NRC Handelsblad* 22 oktober 2016.

Wert, G. de & W. Dondorp, 'Voor oprukkende gentechniek zijn strenge regels nodig'. In: *NRC Handelsblad* 18 december 2018.

www.nrc.nl/nieuws/2018/12/17/voor-oprukkende-gentechniek-zijn-strenge-regels-nodig-a3060958

Bibliography – Part II

Bates Ramirez, V. 'Designer babies, and their babies: how AI and genomics will impact reproduction'. Website SingularityHub, 14 november 2018.
singularityhub.com/2018/11/14/designer-babies-and-their-babies-where-ai-and-genomics-could-take-us/#sm.00184skat1dgod8ppj61mdr7hxulc

Beers, B. van, 'We zijn blij met de assemblage van onze iZoon' In: *De Groene Amsterdammer* 8 februari 2018.
www.groene.nl/artikel/we-zijn-blij-met-de-assemblage-van-onze-izoon

Begley, S. 'Fertility clinics around the world asked 'CRISPR babies' scientist for how-to help'. Website STAT, 28 mei 2019.
www.statnews.com/2019/05/28/fertility-clinics-asked-crispr-babies-scientist-for-how-to-help/

Bredenoord, A., W. Dondorp & G. de Wert, 'Synthetische embryo's stellen de wet op proef'. In: *De Volkskrant* 7 mei 2018.
www.nrc.nl/nieuws/2018/05/07/synthetische-embryos-stellen-de-wet-op-de-proef-a1602140

COGEM & Gezondheidsraad (2016). *Trendanalyse biotechnologie 2016. Regelgeving ontregeld*. Bilthoven: COGEM.

Dijck, R. van, 'De kinderen van Karbaat'. In: *NRC Handelsblad* 4 juli 2019.
www.nrc.nl/nieuws/2019/07/04/de-kinderen-van-karbaat-a3965797

Garderen, F. van & S. Vanderkerckhove 'Kinderwens? Voor ruim 1.000 euro kan u achterhalen of u drager bent van 1.200 erfelijke ziektes'. Website De Morgen, 23 juli 2019. www.demorgen.be/nieuws/kinderwens-voor-ruim-1-000-euro-kan-u-achterhalen-of-u-drager-bent-van-1-200-erfelijke-ziektes~bb2dafddc/

Gezondheidsraad (2016). *Prenatale screening*. Den Haag: Gezondheidsraad.

Gils, S. van, 'Designbaby op komst?'. In: Het Financieele Dagblad 19 januari 2019.
fd.nl/futures/1285708/designbaby-op-komst#

Global Market Insights 'Assisted Reproductive Technology (ART) market size worth USD 31 billion by 2023'. Website Global Market Insights, 5 juli 2016.

www.globenewswire.com/news-release/2016/07/05/853690/0/en/Assisted-Reproductive-Technology-ART-Market-size-worth-USD-31-Billion-by-2023-Global-Market-Insights-Inc.html

Jasanoff, S. & B. Hurlbut (2018). 'A global observatory for gene editing'. *Nature* 555, pp. 435-437.

Kamerstukken II, 2016/17, 29323, nr. 110.

Kamerstukken II 2017/2018, 34990, nr. 1.

Keulemans, M., 'De voortplanting gaat radicaal veranderen' In: *De Volkskrant* 9 juni 2018.

www.volkskrant.nl/wetenschap/de-voortplanting-gaat-radicaal-veranderen~b176bf81

KNOV 'NIPT beschikbaar voor alle zwangeren: resultaten eerste jaar'. Website Koninklijke Nederlandse Organisatie van Verloskundigen, 18 juni 2018.

www.knov.nl/actueel-overzicht/nieuws-overzicht/detail/nipt-beschikbaar-voor-alle-zwangeren-resultaten-eerste-jaar/2346

Kragten, T., 'Genetische longziekten 'wegknippen' uit het DNA van een foetus. Kan dat straks ook bij mensen?' In: *De Volkskrant* 17 april 2019.

www.volkskrant.nl/wetenschap/genetische-longziekten-wegknippen-uit-het-dna-van-een-foetus-kan-dat-straks-ook-bij-mensen~b5cb083e/

Lander, E. et al. (2019). 'Adopt a moratorium on heritable genome editing'. *Nature* 567, pp. 165-168.

Ledford, H. (2016). 'Titanic clash over CRISPR patents turns ugly'. *Nature* 537, pp. 460-461.

Liang, P. et al. (2015). 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes'. *Protein & Cell* 6, nr.5, pp. 363-372.

Ma, H. et al. (2017). 'Correction of a pathogenic gene mutation in human embryos'. *Nature* 548, pp. 413-419.

Cyranoski, D. (2019). 'Russian biologist plans more CRISPR-edited babies'. *Nature* 570, pp. 145-146.

Mastenbroek, S. & S. Repping 'Laat het verbod op embryokweek los'. In: *NRC Handelsblad* 4 december 2018.

www.nrc.nl/nieuws/2018/12/03/laat-het-verbod-op-embryokweek-los-a3009216

Metzl, J., 'Making babies in the year 2045'. In: *The New York Times* 10 april 2019.

www.nytimes.com/2019/04/10/opinion/genetic-testing-privacy.html

Molteni, M. 'Now you can sequence your whole genome for just \$200'. Website *WIRED*, 19 november 2018.

www.wired.com/story/whole-genome-sequencing-cost-200-dollars/

PGD Nederland 'Wat is PGD? Landelijke indicatiecommissie PGD'. Website PGD Nederland, geraadpleegd op 11 maart 2019.

www.pgdnederland.nl/landelijke-indicatiecommissie-pgd

Regeling preïmplantatie genetische diagnostiek (2009, 16 februari). Geraadpleegd op 11 maart 2019, van zoek.officielebekendmakingen.nl/stcrt-2009-3177

Regalado, A. 'A third CRISPR baby may have already been born in China'. Website MIT Technology Review, 2 juli 2019.

www.technologyreview.com/s/613890/a-third-crispr-baby-may-have-already-been-born-in-china

Sheridan, C. 'Go-ahead for first in-body CRISPR medicine testing'. Website Nature Biotechnology, 14 december 2018.

www.nature.com/articles/d41587-018-00003-2

Staats, L., 'Hebben we recht op een kind?'. In: *De Volkskrant* 12 april 2018.

www.volkskrant.nl/columns-opinie/opinie-hebben-we-recht-op-een-kind~b67099d3/

Stelling, T. 'Kinderwens? Laat je niet gek maken door de ivf-industrie'. Website De Correspondent, 19 september 2018.

decorrespondent.nl/8702/kinderwens-laat-je-niet-gek-maken-door-de-ivf-industrie/511145333468-3ba9b09e

Stelling, T. 'Hoe we kinderen bleven uitstellen en zo een monster baarden: de baby-industrie'. Website De Correspondent, 23 mei 2018.

decorrespondent.nl/7338/hoe-we-kinderen-bleven-uitstellen-en-zo-een-monster-baarden-de-baby-industrie/431025563892-4ec27bb3

Stetka, B. 'A Genetic Risk Score Tries to Predict Whether a Child Will Become Obese'. Website Scientific American, 18 april 2019.
www.scientificamerican.com/article/a-genetic-risk-score-tries-to-predict-whether-a-child-will-become-obese/

TNO 'personalised nutrition is meer dan voeding afgestemd op je genen'. Website TNO, 12 oktober 2018.
www.tno.nl/nl/tno-insights/artikelen/personalised-nutrition-is-meer-dan-voeding-afgestemd-op-je-genen/

Vaessen, T., 'D66 maakt de weg vrij voor industriële fabricage baby's'. In: *Het Financieele Dagblad* 23 december 2017.
fd.nl/weekend/1229975/d66-maakt-weg-vrij-voor-industriele-fabricage-van-baby-s

Veen, M. 'Donorkinderen gedupeerd, spermadonoren alsnog anoniem' Website NOS, 4 maart 2019.
nos.nl/nieuwsuur/artikel/2274500-donorkinderen-gedupeerd-spermadonoren-alsnog-anoniem.html

Veerman, E. 'De baby-industrie'. Website De Kennis van Nu, 8 juli 2011.
dekennisvannu.nl/site/artikel/De-baby-industrie/5482

Verhoef, P. (2018). 'Los het tekort aan eicellen niet op met schimmige handel'. *Podium voor Bioethiek* 25, nr. 3, pp. 6-9.

Vermeulen, M. & T. Verkade 'Er is een Nederlands kindeke geboren op aard (uit een Mexicaanse draagmoeder, met een Amerikaanse eicel)'. Website De Correspondent, 26 december 2015.
decorrespondent.nl/3812/er-is-een-nederlands-kindeke-geboren-op-aard-uit-een-mexicaanse-draagmoeder-met-een-amerikaanse-eicel/223912435208-63f99d33

Voormolen, S. & C. Berthelot, 'Geboren in de babyfabriek- de techniek is bijna zover' In: *NRC Handelsblad* 27 januari 2018.
www.nrc.nl/nieuws/2018/01/26/geboren-in-de-babyfabriek-a1589934

Wassink, J., 'Behoedzaam voorwaarts met CRISPR-Cas'. In: *De Groene Amsterdammer* 16 mei 2018.
www.groene.nl/artikel/de-evolutie-in-eigen-hand

Wert, G. de & W. Dondorp, 'Voor oprukkende gentechniek zijn strenge regels nodig'. In: *NRC Handelsblad* 18 december 2018.
www.nrc.nl/nieuws/2018/12/17/voor-oprukkende-gentechniek-zijn-strenge-regels-nodig-a3060958

World Health Organization (2019). *Statement on governance and oversight of human genome editing*.
www.who.int/news-room/detail/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing

Wouters, M. & V. Rerimassie (2017). *De Burger aan het Woord: publieksopvattingen over moderne biotechnologie*. Capelle aan den IJssel: InSites Consulting

Appendix 1: List of interviewees

Name	Organisation & position
Kirsten van Spronsen	Erfocentrum – Communications adviser
Jeroen Wiegertjes	NEMO Kennislink – Manager, Scientific Communication
Robert Hofstra	Erasmus MC – Professor of Human Genetics / Head of Clinical Genetics Department
Geert Hamer	Amsterdam UMC – University lecturer
Dual interview: -Lidewij Henneman -Ivy van Dijke	Netherlands Association of Community Genetics and Public Health Genomics (NACGG) -Board member (chair) -Board member
Martina Cornel	Amsterdam UMC – Professor of Community Genetics and Public Health Genomics
Diederik van Dijk	NPV – Director
Dual interview: -Marjolein Kriek -Gijs Santen	Leiden University Medical Centre (LUMC) -Clinical genetician -Clinical genetician
Dual interview: -Wendy Rodenburg -Korienke Smit	National Institute for Public Health and the Environment (RIVM), Centre for Health Protection, Centre for Safety of Substances and Products, Department of Gene Technology and Biological Safety -Scientific advisor -Policy advisor & Coordinator Safe-by-Design in education
Cor Oosterwijk	Dutch Patient Alliance for Rare and Genetic Diseases (VSOP) - Director
Dual interview: - Martine Bouman - Roel Lutkenhaus	Center for Media & Health (CMG) -Scientific director, Center for Media & Health and Professor of Entertainment Media and Social Change, Erasmus University -Media strategist and researcher
Jan van de Venis	The Worldconnectors – Ombudsperson Future Generations
Arend Jan Waarlo	University of Utrecht, Emeritus VSOP Professor of Personal and Social Opinion Formation on Heritability and Health / COGEM, member of subcommittee for ethical and social aspects
Gerard Hilhorst	Dutch Association of Little People - member

Appendix 2: Participants in scenario workshop

Participant	Affiliation
Edwin Cuppen	UMCU, Center for Molecular Medicine, Genetics section
Alwin Derijck	Amsterdam UMC – Location AMC, Center for Reproductive Medicine; Registered member of Dutch Society for Clinical Embryology
Bernard Roelen	University of Utrecht, Department of Farm Animal Health
Susana Chuva de Sousa Lopez	LUMC, Department of Anatomy and Embryology
Marianne Boenink	University of Twente, Philosophy
Britta van Beers	Vrije Universiteit Amsterdam, Department of Legal theory and history
Peter Joosten	Science journalist and publicist (peterjoosten.net)
Adriana Kater-Kuipers	Erasmus University, Medical Ethics
Sam Riedijk	Erasmus MC, Clinical Genetics Department
Karin Diderich	Erasmus MC, Clinical Genetics Department
Lianne Ruitenbeek	NPV – Zorg voor het leven
Marc van Mil	UMCU, University of Utrecht, Biomedical Sciences
Ruth Mampuys	Commission on Genetic Modification (COGEM), Erasmus School of Law
Michelle Habets	Rathenau Institute
Dirk Stemerding	Independent researcher, Biotechnology and Society
Diewertje Houtman	Erasmus MC, Clinical Genetics Department

Appendix 3: The methodology of the future scenarios

Time span

The future scenarios at the end of this report are set in in 2039, twenty years from now. This is far enough into the future to disengage from the current situation, but is not an 'unreachable future'. Twenty years is still within the life expectancy of most people living today. At the same time, it is far enough into the future for the first genetically modified babies – who were born in China in 2018 – to have grown into young adults. In 2039, they will be 21 and might already have their own children by then.

It is conceivable that within this period of twenty years laboratory research will be conducted into genetic modification of embryos, and that (clinical) research will be conducted that leads to the birth of genetically modified children and that modification of DNA in human embryos will have become a realistic option in medical reproductive practice.

Question

The key question in writing the future scenarios was this: what might society look like in relation to health, healthcare, well-being, pregnancy and reproduction in twenty years' time? And what role will genome-editing technologies to modify the DNA of future children play in that regard?

To answer that question, we considered the following specific issues.

1. What developments and events in the field of science and technology could influence the use of genome-editing technologies to modify the DNA of future children?
2. How might the science and practices relating to pregnancy and reproductive health have developed as a result of the availability (to a greater or lesser extent) of new reproductive technologies – and in particular genome-editing technologies to modify the heritable DNA of future children?
3. How might the science and practices relating to pregnancy and reproductive health be economically organised (in other words, the economic system surrounding these practices)?
4. How might germline genome editing be regulated at the national and international level? And what might be the consequences if there is no international level playing field?

5. What influence might the availability of genome-editing technologies for the modification of the DNA of future children have on the norms and values relating to reproduction, healthcare and well-being? And vice versa, what influence might those standards and values relating to reproduction, healthcare and well-being have on the availability or otherwise of those technologies, and in what way?

There were six steps in the process of writing the scenarios as we explain below.

1. Desk research and interviews with experts

We conducted desk research and interviewed experts to produce an overview of relevant developments. We also considered social and ethical dilemmas relating to the development, introduction and use of genome-editing technologies to modify the DNA of future children in various practices relating to reproduction, health, healthcare and well-being. A bibliography and the names of the experts can be found at the end of part 1 of this report and in appendix 2. A scenario workshop was held to generate further input and to explicate the scenario's (see point 6).

The main trends and developments were identified and described based on the desk research and the interviews with experts. They were then classified under six variables:

- science and technology;
- national laws and regulations;
- international laws and regulations;
- practices relating to pregnancy and reproductive healthcare;
- the economic organisation of science;
- social developments.

2. Identification of the driving forces behind these developments

The various trends and developments are driven by 'driving forces' such as geopolitical relationships and changing norms and values in relation to pregnancy and reproduction. To formulate provocative but plausible futures, these driving forces had to be identified and described. In the next section we describe the nature of the driving forces behind the developments presented in the scenarios.

3. Identification of two key variables

In order to formulate clearly distinct scenarios that also reflect variations in the development of society (including the effects on various practices), two key variables were chosen. These key variables have a high degree of uncertainty and a high impact on the future worlds that are sketched.

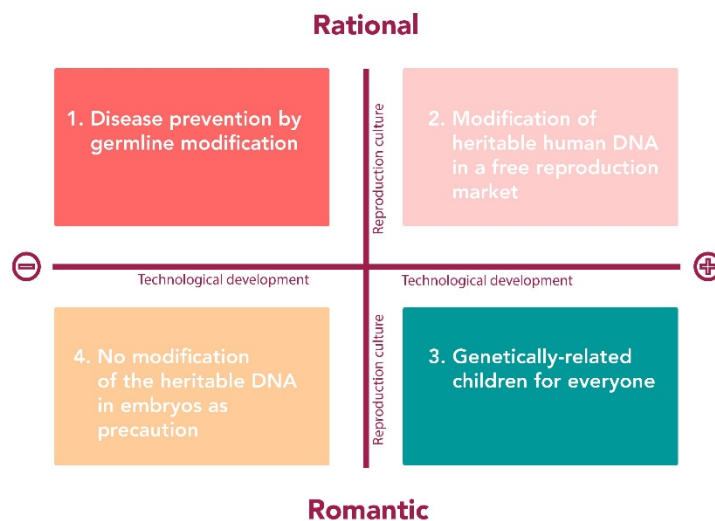
The following key variables were chosen based on the desk research and the interviews with experts:

- The pace (and success) at which **the science and technology** relating to the use of genome-editing technologies to modify the DNA of future children advances.
- The **cultural dimensions of reproduction and pregnancy**. These could be more **'rational'** (with the emphasis on controlling risks and optimising the ratio of costs to benefits) or more **'romantic'** (with the emphasis on naturalness, personal growth and a holistic approach to health, pregnancy and reproduction).

4. Four quadrants

The two key variables were arranged into four quadrants (see figure 4). For each quadrant, a rough version of a scenario was written based on the six variables described above (with their own developments) and the underlying driving forces. Figure 5 explains the various steps involved in drafting the scenarios.

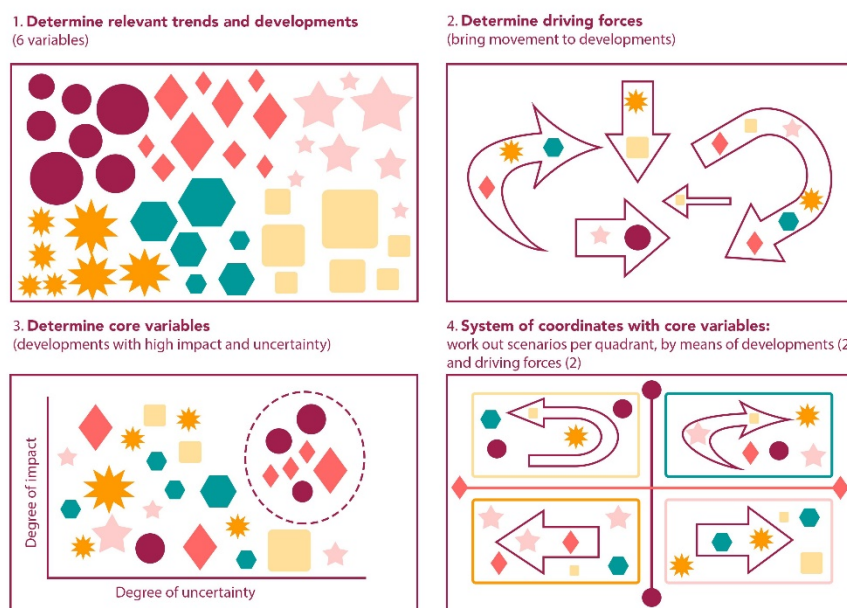
Figure 4 The scenarios in four quadrants



5. Scenario workshop

During a workshop with sixteen experts from different backgrounds (in disciplines such as healthcare, science, ethics and philosophy), the rough scenarios were refined and elaborated. In the first of two sessions, the content of each scenario was fleshed out, while the second was devoted to a discussion of the ethical and social dilemmas in each scenario. A list of the participants in the workshop can be found in appendix 2.

Figure 5 The steps in the scenario approach



Source: Rathenau Institute

The driving forces

Various driving forces influence the six variables that we described earlier (science and technology; national laws and regulations; international laws and regulations; practice in relation to pregnancy and reproductive health; the economic organisation of science; social developments). In turn, these variables influence whether and, if so, how genome-editing technologies will be used to modify the

DNA of future children. They also influence the embedding of the technologies in reproductive and scientific practices. We identified five important driving forces of developments (trends) in the six variables.

The first is the desire to prevent suffering. Serious heritable disorders can cause considerable suffering that could perhaps be prevented by modifying the genes of a future child using genome-editing technologies. This possibility is an important driving force behind recent scientific developments and plays a major role in their ethical justification. In that case, germline genome editing is proposed as a preventive, health-enhancing measure. On the other hand, the aim of preventing suffering can also slow the introduction of genome-editing technologies. germline genome editing can have unintended, harmful effects for future children and generations. According to many experts, it must, therefore, be used with a great deal of caution and must be subject to strict requirements in terms of its safety and effectiveness. The extent to which efforts will be made to prevent suffering in future children by modifying heritable DNA depends, among other things, on the perceived moral obligation to prevent such suffering – on the part of parents towards their future children, of the government towards the general public and of care professionals towards their patients. The scientific community also feels a moral obligation in this regard.

A second driving force is the competitive culture in international science (Rathenau Institute, 2018), which prompts scientists to seek 'breakthroughs' and to be the first to make a discovery, and creates pressure to constantly conduct new experiments and publish the results. In the current system, individual scientists are to a large extent judged on the volume of their output. This competitive culture can conflict with the rigour and careful reflection on the broad social consequences of research.

Moreover, there is competition between countries to be leaders in the field of science, or at least not to fall too far behind, for fear of 'missing the boat' and weakening their knowledge position. There is an active international community of scientist and scientific organisations engaged with germline genome editing and CRISPR-Cas9. For example, two Global Summits on Human Gene Editing were organised in 2015 and 2018, at which new developments in the modification of heritable human DNA were discussed. At the same time, there was also deliberation on its possible consequences and the conditions it should have to meet.⁵³ However, the discussions in the international arena were unable to prevent the Chinese researcher He Jiankui from announcing in 2018 that he had modified the genome of two babies.

53 See <http://nationalacademies.org/gene-editing/index.htm> and [/www.nationalacademies.org/gene-editing/2nd_summit](http://www.nationalacademies.org/gene-editing/2nd_summit).

A third driving force is the industry that has grown around reproduction and fertility (Veerman 2011; Stelling, 2018). Fertility and reproductive technology generates substantial revenues worldwide. In most countries, many fertility clinics are private enterprises (the Netherlands is an exception in that respect). The industry has an interest in serving and creating the largest possible market by offering numerous products and services, rather than only effective medical care, as is the goal in the Netherlands (Mastenbroek & Repping, 2018). Many of the commercial reproductive treatments that are offered have not been proven effective, or have even been shown to be ineffective. Although experts question the utility and necessity of such treatments, the supply and use of those treatments is growing worldwide. Within a week of the announcement of the birth of the first genetically modified babies, the Chinese scientist was contacted by fertility clinics, in Dubai for example, requesting his help in introducing genetic modification of embryos in the range of services they offered to prospective parents (Begley, 2019).

A fourth driving force is the desire of parents to have healthy, genetically related children. Prospective parents can be willing to pay a lot for that. Many parents also make choices on the basis of 'wanting the best for your child'. That conviction spurs them to protect their child from serious heritable disorders (De Wert & Dondorp, 2018). Connected with the desire for a healthy, genetically-related child, is the question of the views in society regarding the legitimacy of that desire. In today's society, having a healthy, genetically related child is regarded as a legitimate desire, for which medical treatment should be available (and financed), if necessary.

A final factor is the perception of the influence of DNA on our body and our life. Knowledge of the influence of genes on personal attributes, disease and health is increasing all the time. The general public also have greater access to genetic tests that provide them with personal genetic information. However, people's ideas about the genetic basis of their traits are influenced in part by reports in popular media and by the growing number of commercial enterprises that offer DNA tests to establish traits (intelligence, the optimal diet, etc.). As a result, some people exaggerate the extent to which their life and body is determined by their DNA, and, therefore, possibly also over-estimate the possibilities of altering them by modifying heritable DNA.

The same applies to a sometimes overly simplistic view of the technology itself: the impression created by the description 'CRISPR as cut-and-paste in DNA' might be too optimistic with regard to the risks and possibilities of the technology. Public perceptions of other applications of gene-editing technology (in agriculture, for instance) also influence expectations and opinions among the general population (Wouters & Rerimassie, 2017). Public perceptions can vary greatly from those of experts.

Developments in each variable

In this section, we describe the relevant trends and developments in relation to germline genome editing for six variables:

- science and technology
- national laws and regulations
- international laws and regulations
- practice relating to pregnancy and reproductive medicine
- the economic organisation of science
- social developments

These variables influence whether, and if so how, genome-editing technologies will be used for germline genome editing. They also have an impact on the embedding of those technologies in reproductive and scientific practices. Most of the trends and developments were identified from the same literature as was consulted for part 1 of this report and the interviews with experts described in chapter 3. Consequently, some of the information will overlap with the content in part 1, but we have added an extensive description to ensure that this section can also be read separately.

Science and technology

The genome-editing technology CRISPR-Cas9 is a hot topic in biomedical research today (COGEM & Health Council of the Netherlands, 2016). CRISPR is used as a research tool, for example to explore gene expression and the function of genes. The technology itself is also the subject of research, with the aim of optimising it. CRISPR has a wide range of potential applications. Frequently mentioned areas of application are bacteria, plants (agriculture), animals (livestock, test animals), adults (gene therapy) and embryos (germline genome editing). Research in different areas of application could be mutually reinforcing (if findings and breakthroughs in one area can also be applied in another), but could also curb progress (in the event of incidents or disappointing results).

In addition to research into DNA modification in embryos, research in humans is also being conducted into somatic gene therapy: the treatment or cure of diseases by altering the DNA of cells. Meanwhile, with CRISPR-Cas9, researchers have been able (*in vitro* – thus not in living humans) to cure cystic fibrosis in lung cells, repair blood cells with sickle cell disease (a recessive heritable disorder caused by abnormal haemoglobin) and remedy Duchenne disease (a serious heritable muscular disorder) in muscle cells (Wassink, 2018). In the US, permission was granted at the end of 2018 for a clinical trial (in other words, in living humans) of a treatment for hereditary blindness with CRISPR-Cas9. The American Food and Drug Administration (FDA) also approved a treatment for thalassemia (a heritable blood disorder), which involves genetically editing blood stem cells outside the body

and then putting them back in the body (Sheridan, 2018). A challenge in this context is to reach a sufficient number of cells with CRISPR-Cas9 and to correctly edit each cell individually. Researchers in the US were recently able to cut out a mutation that causes cystic fibrosis from the DNA in the lungs of the foetus of a mouse. With this procedure, the disease could be prevented before birth without making heritable changes in the DNA.

Recent research into germline genome editing

germline genome editing, the subject of this report and the public dialogue, differs from somatic gene therapy in that genes are modified in reproductive cells (egg or sperm cells) or an early embryo (very recently fertilised egg). Every cell that grows from them will, therefore, contain the change that has been made in the DNA. The baby that is born from such an embryo will, therefore, have a modified genome, in all of his or her cells, including the reproductive cells. In the event of procreation, the offspring of that baby will, therefore, inherit the modified gene.

In April 2015, researchers in China conducted the first experiments to modify the DNA of (non-viable) human embryos with CRISPR-Cas9 (Liang et al., 2015). In 2017, researchers in the United States succeeded for the first time in 'repairing' a defective gene in an embryo (Ma et al., 2017). And in November 2018, the Chinese researcher He Jiankui reported that twins had been born from an embryo whose genes he had edited in the laboratory (Regalado, 2018). There are now rumours that a third genetically modified baby has been born (Regalado, 2019) and a Russian scientist has announced that he wants to make more genome-edited babies (Cyranoski, 2019).

Alternative technologies

Besides the developments in the field of heritable human DNA editing, other scientific advances that could also cause significant changes in reproduction in the future are simultaneously being made in reproductive medicine (Keulemans, 2018). Relevant examples are:

- in vitro gametogenesis (IVG): the reprogramming of cells into reproductive cells in the laboratory (Van Beers, 2018);
- the cultivation of egg cells from ovarian tissue;
- the creation of 'synthetic embryos' – structures of embryonic or re-programmed stem cells with embryo-like features (Bredenoord, Dondorp & De Wert, 2018);
- artificial wombs;
- increased possibilities for genetic screening, such as *whole genome sequencing* or screening for carrier status (Metzl, 2019).

These techniques could have a major impact, particularly in combination with each other. If egg and semen cells can be produced easily with IVG, it will be possible to create large numbers of embryos with donor cells that can be cultivated. The entire

genome of all these embryos could be screened with new sequencing and analytical techniques. Once any genetic modifications have been made, the embryo with the best gene package would then be transferred to the womb (Van Beers, 2018).

If one innovation is slowed or prohibited by legislation, scientists might focus more on developing alternatives, which would then be adopted in practice sooner. Earlier restrictions on the use of embryonic stem cells for research contributed to the development of induced pluripotent stem cells (IPS), for example.⁵⁴ Parallel research areas are, therefore, closely connected and can influence one another in complex ways.

For instance, if egg and semen cells can be produced from skin cells with IVG, embryos could be created on a large scale. That could have a major impact on the use of embryo selection. With embryo selection, embryos that do not display particular genetic abnormalities are selected. The more embryos there are to choose from, the greater the chance parents have of finding an embryo that is not ill or a carrier. At present, egg and semen cells first have to be acquired from the prospective parents.

Acquiring egg cells is a time-consuming and burdensome process with risks for the woman's health. The procedure generally produces between eight and ten cells, which means that no more than that number of embryos can be created. If more embryos can be created, there is a greater chance that they will include an unimpaired embryo. If IVG makes it possible to produce hundreds, or even thousands, of embryos instead of just ten, that will increase the chance that there will be an embryo that does not have particular undesirable genes and does have other desirable genes amongst them. In some cases, this could be an alternative to modifying genes in embryos.

The success rate of IVF is also improving slightly every year (Voormolen & Berthelot, 2018). If that trend continues, more fertile couples who have no serious heritable disorder could start seeing IVF as a realistic option, since it would also give them access to pre-implantation diagnosis, possibly in combination with selection or the modification of heritable DNA with genome-editing techniques. In this way, they can avoid an embryo with undesirable genetic properties or actually choose an embryo with the desired genetic properties.

Developments in the field of artificial intelligence (AI) and big data analysis will also play a role in the development of germline genome editing – particularly in terms of

⁵⁴ These are cells that are reprogrammed, as it were, so that they behave almost identically to embryonic stem cells. In principle, such cells can differentiate into all cell types.

influencing heritable diseases with a more complex genetic basis, or other non-monogenetic properties such as intelligence or musicality (Bates Ramirez, 2018). The combination and analysis of large volumes of data could help to increase understanding of the genetic basis of such complaints and attributes (Stetka, 2019). Furthermore, it is becoming cheaper to have your entire genome mapped: it can now be done for as little as 200 dollars (Molteni, 2018).

Finally, developments are underway that could in time make it possible to apply genome-editing technologies without IVF. One example is *improved genome editing via oviductal nucleic acids delivery*, or i-GONAD (Takbayashi, 2018). In this procedure, the components that are needed for modification are implanted in the uterine tube through a small incision. The membrane of the fertilised cell descending in the uterine tube is then subjected to an electrical pulse in order to increase its permeability so that the genetic modification can be made in the woman's body. The i-GONAD-technology avoids the need for complex *in-vitro* procedures and in some cases makes germline genome editing possible without IVF. But the technology does have some drawbacks. There is no way of checking whether the genetic modification has succeeded before the woman becomes pregnant (the moment when the fertilised cell is nestling in the womb). In addition, the technology is stressful, certainly compared with natural conception.

National laws and regulations

The Embryo Act prohibits the inducement of a pregnancy with germline cells (reproductive cells or embryos) in which the genetic material of the nucleus has been modified (Embryo Act, art. 24 (g)). Also prohibited are the creation of embryos specifically for scientific research (Embryo Act, art. 24 (a)) and allowing an embryo to develop outside the human body for longer than fourteen days (Embryo Act, art. 24 (e)). The first prohibition rules out clinical application of genome-editing technologies for germline genome editing, except where the modified DNA is outside the nucleus of the embryo, as in case of mitochondrial DNA. The second prohibition makes research into genome editing more difficult because for genome-editing technologies to be effective for germline genome editing, the genetic modification must occur in all the cells in an embryo. That is only possible if the embryo consists of just one or a few cells – right after fertilisation – and not with a residual embryo that is several days old and by then has too many cells.⁵⁵ Researchers also often regard the 'fourteen day limit' as an obstacle to their research (Stelling, 2017).

To allow for research into and application of genome-editing technologies for germline genome editing, the law will have to be changed. In 2016, the former

55 See chapter 1 of the report for more information.

Minister of Health, Welfare and Sport submitted a proposal to relax the Embryo Act and allow embryos to be cultivated specifically for research under certain conditions (Kamerstukken II, 2016/17, 29323, 110). Such an amendment would allow research into the germline genome editing with genome-editing technologies in human embryos, as well as other types of research (such as research to learn more about the development of the embryo and research designed to improve IVF). This plan was reversed during the formation of the current government, which adheres to the policy that a public dialogue must first be conducted before such ethically sensitive changes in the law can be debated in the House of Representatives (Kamerstukken II 2017/2018, 34990, no. 1).

Current laws and regulations concerning embryo selection are often mentioned as a model for the policy on the use of genome-editing technologies to modify the DNA of future children. The National Indication Committee (PGD) decides on the disorders for which embryo selection is permitted (PGD Regulation, 2009) and assesses whether applications for new indications fall within the parameters of what is socially and ethically acceptable (PGD Nederland, 2019). An important condition is that the intention must be to prevent a serious, heritable disorder. The regulation of embryo selection has successfully prevented a slippery slope towards human enhancement in recent years. However, there is disagreement about whether this would also be the case with similar regulation of genome-editing technologies for germline genome editing because, in theory, germline genome editing has a greater capacity for human enhancement than embryo selection. Embryo selection could theoretically be used to select desirable traits, such as intelligence, but the possibilities are far more limited, because there are only around ten embryos to be selected from for each treatment and because the genome of these embryos is created through natural recombination of the existing genetic material of the prospective parents. With germline genome editing, by making targeted modifications an embryo could be created with a genome that could never realistically have been created by natural recombination. In theory, it would also be possible to create genetic variants that do not occur naturally (see, for example, Van Gils, 2019).

International laws and regulation

At present there are no international laws and regulations that permit the clinical application of heritable human DNA editing. The international landscape in terms of legislation and regulation is a patchwork of countries with strict regulation (or prohibition), countries with a conditional prohibition or rules of conduct (which are not legally binding), countries with unclear regulations, and countries without any relevant regulations (Van Gils, 2019). Meanwhile (especially since the birth of the first genetically modified babies in China), there have been growing calls for broad harmonisation of laws and regulations. For example, various proposals have been

made to establish committees and consortia to organise international oversight of germline genome editing. Last year, the sociologists Sheila Jasanoff and John Hurlbut called for a global observatory for genome editing, an international network of academics and organisations that would support and embark on a broad global dialogue (Jasanoff & Hurlbut, 2018).

A number of leading scientists recently called for a global moratorium on the clinical application of germline genome editing. They called for national (or European) decision-making to be embedded in a worldwide framework that ensures that national decision-making processes are rigorous, transparent and the subject of debate (Lander et al., 2019). In addition, the World Health Organization (WHO) has formed an advisory committee of experts to develop worldwide standards for governance and supervision of heritable human DNA modification. The committee issued a statement calling on regulatory or ethical bodies in every country not to give permission for human germline genome editing until further notice.

At the same time, new technology takes little notice of national borders. It is already evident that prospective parents and scientists travel abroad to avoid restrictions on the use of reproductive technologies (including controversial treatments) in their own country (Vermeulen & Verkade, 2015; Stelling, 2018b). Competition between countries to be the first to implement germline genome editing could also form a barrier to harmonisation of legislation and regulation.

The practice relating to pregnancy and reproductive medicine

Human reproduction has not been confined to the bedroom for a long time. The supply and use of assisted reproductive technologies are increasing. For example, a wide variety of new methods of assisted human reproduction have emerged in recent years, such as pregnancies with the help of donated reproductive cells, IVF and surrogacy (Stelling, 2018a, Stelling, 2018b). In addition, the indication for the use of IVF has gradually expanded. Whereas it was originally only offered to women who could not get pregnant because of blocked fallopian tubes, nowadays it is also prescribed to women who have no such specific biological complaint, but who are for some inexplicable reason unable to have a child (80% of all IVF patients). It is not known whether there is a higher chance of success with IVF than waiting for a spontaneous impregnation for this group of women (Stelling, 2018a).

The practice relating to pregnancy and reproductive medicine offers increasing possibilities for genetic screening – prior to conception (screening for carrier status), before a pregnancy (within in-vitro embryos), during pregnancy (prenatal tests such as NIPT), and after birth (the neonatal heel prick, for example). The trend is to arrange screenings sooner, more often and for more disorders. In the Netherlands, couples can already be tested for 70 serious heritable diseases even before a

pregnancy. These tests can be carried out in the UMCG⁵⁶ and in the medical centres in Amsterdam.⁵⁷ In Belgium, has recently been made possible to screen for 1,200 heritable diseases (Van Garderen & Vanderkerckhove, 2019). Prospective parents often pay for these tests themselves. In 2016, the Health Council of the Netherlands recommended that every pregnant woman should be offered an additional ultrasound scan at 13 weeks, in addition to the scan to screen for structural abnormalities after around 20 weeks of pregnancy (Health Council of the Netherlands, 2016).

Such tests for carrier status and structural ultrasound scans offer prospective parents the possibility to establish the existence or an increased risk of a heritable disorder at various times before and during pregnancy. Depending on the test results, they can then choose whether or not to proceed with a pregnancy. Hoping for a healthy child then becomes choosing to have one.

Economic organisation of science and reproductive medicine

There is an extensive international reproductive industry with an interest in offering prospective parents a wide range of treatments and constantly introducing new treatments that 'increase the chance of pregnancy'. The effectiveness of these treatments has often not been properly investigated, and some have even been proved to be ineffective. The Netherlands is an exception in many respects, because reproductive treatments in the Netherlands are part of the regular healthcare system – and are, therefore, not provided in private clinics. They are usually reimbursed under the basic health insurance package. But even in the Netherlands, new reproductive technologies are occasionally used without rigorous prior research into their effectiveness and safety. A well-known example is IVF (Mastenbroek & Repping, 2018).

Science, healthcare and business are intertwined, although the extent differs from one country to another. The links are not as close in the Netherlands as in the United States, for example. Scientific developments could lead to highly profitable biotechnological products. For example, the American market research firm *Global Market Insights* (2016) estimates that the global market for artificial reproductive technology will be worth around 31 billion dollars in 2023. An example of this is the lengthy patent war that is unfolding around CRISPR-Cas9 (Ledfort, 2016 & Begley, 2019). Various gene technologies are patented and could generate substantial revenues.

56 See www.umcg.nl/NL/UMCG/Afdelingen/Genetica/patienten/erfelijkheid/dragerschapstest/Paginas/default.aspx

57 See www.dragerschapstest.nl.

Medical tourism for the purposes of reproduction has now become a familiar phenomenon. Couples in the West who want a child and can afford it can travel to other – often less prosperous – countries for treatments, services and ‘products’ that are prohibited in their own country. The options include:

1. Egg cells: even in Europe there is a trade in egg cells from countries with less strict rules (for example, Spain and Romania); Dutch couples also engage in it (in the absence of available donor cells) (Verhoef, 2018).
2. Surrogate mothers: commercial surrogacy is not permitted in the Netherlands; in other countries, women can earn a lot of money as surrogate mothers (Vermeulen & Verkade, 2015).
3. Wealthy parents can also travel to various places in the world to fulfil other wishes. For example, in the United States they can buy an egg cell from a woman who is performing well at university for 20,000 to 30,000 dollars, or can have embryos selected on the basis of gender (Vaessen, 2017).

A debate has also arisen in recent years about the ‘baby industry’ (Staats, 2018). The reasons for this include the various malpractices that have come to light in connection with adoption in countries such as Brazil, Colombia, Indonesia, Sri Lanka and Bangladesh (NOS, 2018). It has also been found that not knowing who their biological father is can cause stress in children of sperm donors (Veen, 2019). Fertility specialists and clinics do not always treat reproductive cells and residual embryos with care after an IVF treatment. The best known example of this is the Dutch fertility specialist Jan Karbaat, who was found to have fathered at least 53 children by mixing his own semen with donor semen (Van Dijck, 2019).

Social developments

There is growing attention in the healthcare sector and in society to preventing diseases and stimulating general well-being. In 2018, for example, a National Prevention Agreement was made with the aim of reducing smoking, obesity and alcohol consumption.⁵⁸ Programmes have also been launched to help people tune their lifestyle to their genes, for example with ‘personalised nutrition’ (TNO, 2018). There are also various programmes to help mothers to live healthily during pregnancy and so reduce infant mortality and give children a ‘promising start’.⁵⁹ There are also various websites that provide information for prospective parents; an example is *strakswangerworden.nl*, which was launched in 2012 at the request of the Ministry of Health, Welfare and Sport.

Human reproduction and pregnancy, and how they are experienced, are increasingly managed and influenced by technology. Consequently, human reproduction could increasingly assume the character of the *production of humans*.

58 www.rijksoverheid.nl/onderwerpen/gezondheid-en-preventie/nationaal-preventieakkoord

59 www.rijksoverheid.nl/onderwerpen/zwangerschap-en-geboorte/verbeteren-zorg-rondom-zwangerschap

A child is increasingly seen as a product, as something that you design and produce and which has to meet certain quality requirements, and less as something that you are 'given'. This production paradigm can be seen in the 'wrongful birth' and 'wrongful life' actions⁶⁰ that are being brought against reproductive clinics around the world.

In such cases, physicians are accused of not providing parents with sufficient information about their genetic risks or of failing to inform them of the possibilities of genetic diagnosis, so that they could not make an informed choice to become pregnant or to terminate a pregnancy.⁶¹ An example is baby Gammy, a boy with Down syndrome who was born, together with his twin sister Pippa, to a Thai surrogate mother. The children's Australian parents only collected Pippa in the summer of 2014. According to the parents, after a genetic screening the Thai surrogate mother should have had a selective abortion of the foetus with Down syndrome. This resembles a sort of product liability (Van Beers, 2018).

Human suffering as a result of a medical disorder can be detected and prevented sooner than ever. It, therefore, seems increasingly possible to design a perfect life. That raises questions about how far we want to go in pursuit of perfection. In a reaction to perfection, there is also a counter-movement that calls for greater 'acceptance' and 'dealing with the situation'. Because if human life can be engineered to such an extent, what does that say about our respect for 'life on the periphery' or, for example, for professions where strength and practical skills are more important than knowledge and intellect? In relation to pregnancy, we are seeing a move away from medicalisation and towards an emphasis on the naturalness of a pregnancy, for example in magazines⁶² and in the Dutch custom of giving birth at home and without pain relief.

In view of the high costs of certain reproductive technologies and treatments, particularly when they are only available to couples that can travel abroad for them, socioeconomic inequality could increase, both nationally and internationally, and have an impact at the genetic level. Wealthy couples can invest more in their offspring and are, therefore, in a better position to have genetically modified children than their poorer counterparts.

60 In a *wrongful birth* claim, parents hold a care provider responsible for the birth of a child that is 'unwanted', for example because it has a disorder that the physician could have foreseen in advance.

61 A famous example of a *wrongful life* case is the 'baby Kelly case', in which the parents received compensation because their daughter Kelly was born seriously handicapped after the midwife had advised against a prenatal examination despite an increased risk. Baby Kelly herself was also awarded 'compensation' because she has to live with a serious handicap. See also, www.letselschadeslachtoffer.nl/letselschade-jurisprudentie/wrongful-life-arrest.

62 For example, <https://kiind.nl/>

Finally

In part 2 of this report, we presented four future scenarios that could be used in the dialogue, possibly in combination with the vignettes that will be developed by NEMO Kennislink on the basis of these scenarios. In this appendix, we have described how we arrived at the scenarios, including the desk research that underpins the scenarios. This provides sufficient background information for part 2 to be read and used separately. We refer to part 1 of the report for a detailed analysis of the ethical and social issues.

The future scenarios are not predictions of the future but tools and suggestions for reflection on the broad possible consequences for the individual, for the current and future society and for humanity, and for discussion of them during the broad public dialogue on germline genome editing. The scenarios sketch *possible* future developments and present moral and social dilemmas and changing value patterns norms that could play a role going forward.

© Rathenau Institute 2019

This work or parts of it may be reproduced and/or published for creative, personal or educational purposes, provided that no copies are made or used for commercial objectives, and subject to the condition that copies always give the full attribution. In all other cases, no part of this publication may be reproduced and/or published by means of print, photocopy, or any other medium without prior written consent.

Open Access

The Rathenau Institute has an Open Access policy. Reports, background studies, research articles and software are all open access publications. Research data are made available pursuant to statutory provisions and ethical research standards concerning the rights of third parties, privacy, and copyright.

Contact details

Anna van Saksenlaan 51
P.O. Box 95366
2509 CJ The Hague
070-342 15 42
info@rathenau.nl
www.rathenau.nl

Rathenau Institute Board

G. A. Verbeet
Noelle Aarts
Madeleine de Cock Buning
Roshan Cools
Hans Dröge
Edwin van Huis
Erwin Muller
Peter-Paul Verbeek
Marijk van der Wende
Melanie Peters – official secretary

The Rathenau Institute supports the formation of public and political opinion on socially relevant aspects of science and technology. It conducts research on this subject and organises debates on science, innovation and new technology.

Het Rathenau Instituut stimuleert de publieke en politieke meningsvorming over de maatschappelijke aspecten van wetenschap en technologie. We doen onderzoek en organiseren het debat over wetenschap, innovatie en nieuwe technologieën.

Rathenau Instituut