THE DYNAMICS OF REPRODUCTIVE GENETIC TECHNOLOGIES NOW AND IN THE FUTURE

Perspectives of stakeholders

IVY VAN DIJKE

The dynamics of reproductive genetic technologies: now and in the future

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The dynamics of reproductive genetic technologies: now and in the future

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“De omweg is boeiender dan de aankomst”

- Maarten ‘t Hart, de droomkoningin

CHAPTER 1

General introduction and outline of the thesis

Technological developments in the field of reproductive medicine and genetics are increasing the available information for determining a couples' risk of having a child with a genetic disorder, impacting reproductive decision making at different stages [1]. Currently, couples with a known increased risk of having a child with a genetic disorder have several options available to avoid the birth of an affected child. Depending on the aetiology and specific situation, options can include preimplantation genetic testing (PGT), prenatal diagnosis (PND), gamete donation or a decision not to have biological offspring. In the future, affected couples could possibly opt for non-invasive prenatal diagnosis (NIPD) and germline genome editing (GGE) or somatic gene editing (SGE) after the birth of an affected child, further expanding the choices available which may influence reproductive decision making. Besides these options for known genetically high-risk couples, preconception expanded carrier screening (ECS) increases the possibility for couples to determine their risk of having a child with a severe genetic disorder *before* pregnancy. The growing number of options has the potential to complicate an already complex decision-making process and poses major challenges for counselling practices.

Many of these new developments are technology driven, and it is therefore important to attune novel technologies to the desires and viewpoints of the prospective recipients: prospective parents. Ideally, techniques are implemented when they are considered safe, desirable and supported by evidence as best practice. While new technologies could benefit and expand a couples' autonomous decision making, they also raise (new) ethical, psychological and societal issues that call for reflection. This thesis aims to track the dynamics of new developments in reproductive genetic technologies by exploring the perspectives of different stakeholders regarding preconception ECS, NIPD, and GGE, and the possible treatment with SGE, in relation to already existing technologies (PGT and PND).

Genetic disorders and genetic risks

Genetic disorders can be classified as chromosomal, monogenic (caused by a pathogenic variant in a single gene associated with autosomal or X-linked dominant or recessive inheritance), mitochondrial or multifactorial disorders [2]. The risk of having an affected child in every pregnancy depends in part on the pattern of genetic inheritance. For example, for couples who are both carriers of the same autosomal recessive disorder, the risk of having a child with this disorder is 1 in 4 (25%) for every pregnancy. For couples where one parent has an autosomal dominant disorder, the risk of inheritance is 1 in 2 (50%). Chromosome X-linked recessive disorders in general only affect male offspring

(50% chance), while female offspring are healthy carriers or have a less severe manifestation of the disease [2, 3].

Couples with an increased risk of having a child with a genetic disorder often face difficulties when making reproductive decisions, including navigating multiple options currently available, such as PGT and PND, to avoid having an affected child. Several aspects have been shown to influence the reproductive decisions made by high-risk couples and couples without an a priori risk: the perceived severity of the disorder, the perceived risk having a child with a disorder, having children already, the wish to have genetically related children, views towards new reproductive genetic technologies, and individual norms and values, such as the attitudes towards pregnancy termination [4-9]. Understanding the perspectives of when offered or faced with the choice of new (reproductive) genetic technologies, such as NIPD, GGE, and SGE, is relevant for, among others, autonomous reproductive decision-making. Most of these high-risk couples have experience with a disorder that in general few people have, and their attitudes towards current or future impactful technology could inform policy-making and healthcare organization [10]. A key question is whether the growing number of tests made available due to evolving technology will facilitate or hamper the autonomous reproductive decision-making process. Furthermore, implementation of new reproductive genetic technologies needs to be attuned to the needs of society and necessitates investigation into the desirability of new tests and the impact of (potential) additional information and options on decision making. Technologies such as preconception ECS will become increasingly available to prospective parents without an *a priori* high-risk, exploring the perspectives of both high-risk couples and the general public on ECS gives insight into the acceptability of this technology and whether there is a demand.

The reproductive genetic technologies

Reproductive genetic technologies are defined in this thesis as genetic technologies used in the context of reproduction which enable reproductive decision making and/or inform people about their genetic risk of having affected offspring. The technologies discussed below are utilized at different time points: preconception (before pregnancy), prenatal (during pregnancy) and postnatal (after childbirth) as shown in Figure 1. These technologies are currently in different phases of development or implementation in healthcare and practice (indicated with different colours in Figure 1).

Expanded carrier screening

Approximately 1 in 150 couples have an increased risk of having a child with a recessive genetic disorder that could result in a medical disorder [11]. "High-risk" couples are usually identified either after the birth of an affected child, during pregnancy when congenital anomalies are seen by ultrasound and a prenatal diagnosis is performed, by family cascade testing, or through carrier testing. Couples are often unaware of their increased risk and are sometimes informed of this risk by the birth of an affected child. Preconception carrier screening aims to give couples information about their risk of having a child with an autosomal recessive or X-linked disorder to enable them to make an informed autonomous reproductive choice [12]. Carrier screening is preferably offered before conception and not during pregnancy, as more reproductive options are available [13].

Traditionally carrier screening was offered to populations who have an a priori high risk due to the prevalence of one or more autosomal recessive disorders, also called ancestry-based screening. Examples include screening for haemoglobinopathies (sickle cell disease and thalassaemia) in high-prevalence areas [14], screening for Tay-Sachs Disease among Ashkenazi Jewish communities [15] and screening for founder mutations in genetically isolated communities [16].

Due to next-generation sequencing technologies, screening for multiple disorders simultaneously is currently feasible. Worldwide, these expanded carrier screening (ECS) panels are increasingly offered to the general public, regardless of ancestry (universal). In the USA, commercial screening offers are widely available. In Australia, a government-funded research project initiated in 2019 called Mackenzie's Mission aims to screen over 1,000 genes in 10,000 couples [17]. Since 2019, a test panel including 1,200 genes associated with recessive disorders is available commercially in Belgium.

In the Netherlands, carrier screening for the general population is not currently implemented in nationwide healthcare, besides a few local initiatives [18]. In 2016, two academic medical centres in the Netherlands developed an ECS test which is currently available for couples planning a pregnancy. Amsterdam UMC offers a panel of 50 severe early onset autosomal recessive disorders (www.dragerschapstesten.nl) and University Medical Center Groningen (UMCG) offers a couple-based panel for 70 severe childhood onset autosomal recessive disorders via general practitioners in the region (www.umcg.nl/NL/UMCG/dragerschapstest). At UMCG a pilot study was done where general practitioners were trained to offer ECS for, at that time 50 severe childhood onset disorders, to their patient population of reproductive age. It turned out to be a feasible offer and resulted in an informed choice and acceptable psychological outcome for most

patients [19, 20]. These tests cost between €650–1000 and are not reimbursed for couples without a medical indication based on ancestry, ethnicity or consanguinity. Maastricht University Medical Center offers a (reimbursed) panel of more than 2,000 genes associated with known autosomal recessive disorders to consanguineous couples [21]. These ECS tests are not actively offered to all prospective parents; they must be requested.

While studies have been conducted to assess the potential interest in these tests, few have investigated the actual experiences of couples who have chosen ECS [22]. In addition, issues surrounding the demand for such a test and why people would opt for it are unclear [12, 23], highlighting concerns about the actual experiences of test recipients and the impact of expanded screening offers. Results from studies on single-gene or small panels showed negligible negative psychological impact of the tests, especially if participants tested negative [24], although some participants reported an incorrect recall of test results [16, 24]. Nonetheless, psychological impact of an expanded screening panel could be higher, as was suggested in an interview study among pregnant women with positive carrier screening results [25]. One of the aims of this thesis is to investigate the knowledge gap involving the psychological impact of preconception ECS offers in the general population.

Preimplantation genetic testing

If couples are aware of their genetic risk of having a child with a severe genetic disorder for which no effective treatment exists, one of the options available before pregnancy is preimplantation genetic testing (PGT). After in vitro fertilization methods (Intracytoplasmic Sperm Injection (ICSI)), embryotic cells are screened for the specific genetic disorder and after careful genetic diagnosis on embryo-DNA an unaffected viable embryo is implanted in the uterus. A total of three IVF/PGT cycles are currently reimbursed by healthcare in the Netherlands. PGT is available for a number of severe disorders, such as Huntington's disease, spinal muscular atrophy and hereditary breast or ovarian cancer. New requests, for not previously assessed disorders, are reviewed by a national committee (https://www.pgdnederland.nl/). As ECS becomes increasingly available, the requests for PGT are expected to increase, which could potentially challenge current counselling practices, longer waiting lists and new PGT requests [26].

Prenatal diagnosis

Prenatal diagnosis (PND) involves sampling of fetal DNA during pregnancy from the placenta (in chorion villus sampling (CVS)) or from the uterus (in amniocentesis). Genetic analysis of the fetal DNA provides information on the

absence or presence of specific genetic disorders in the fetus so prospective parents can decide to terminate the pregnancy or prepare for a child with a genetic disorder. Eligibility for PND is based on maternal or paternal genetic disorders, genetically high-risk couples, abnormalities in an earlier pregnancy, abnormalities identified during the ultrasound in the first trimester or an abnormal non-invasive prenatal test (NIPT) result. NIPT is a screening test available to all women in the Netherlands to screen for fetal aneuploidy of chromosomes 13, 18 and 21 [27]. Chronic villus sampling is available from 11 weeks' gestation and amniocentesis is available from 15 weeks. Both technologies are invasive and introduce a small miscarriage risk of ~0,2-0,5% [28]. Although this risk is relatively small, it is perceived as substantial by some women [29, 30].

Non-invasive prenatal diagnosis

Apart from non-invasive prenatal testing for aneuploidies, used in screening, NIPD can detect monogenic disorders using fetal DNA in maternal blood [31], as a diagnostic test. In the future, it is likely that NIPD will be available to high-risk couples as risk-free alternative to PND in the Netherlands, and it is already available in several countries worldwide such as the United Kingdom [32-34]. NIPD was initially done for *de novo* disorders detected by ultrasound, such as achondroplasia, and paternally inherited disorders [35]. NIPD is now also used to detect monogenic disorders such as sickle cell disease or cystic fibrosis within families with a known family history. NIPD for autosomal recessive, maternally-inherited dominant disorders and X-linked disorders is still technically challenging[36]. Usually there is no need for confirmation of the test results with invasive testing [37].

Germline genome editing

Although not yet available and heavily debated, another emerging technology is germline genome editing (GGE). Due to the discovery of the gene-editing potential of enzymes involved in bacterial immunity (clustered regularly interspaced short palindromic repeats: CRISPR), it is now possible to efficiently target any region of the human genome for specific editing. With CRISPR technology, the DNA of embryos or germ cells can be modified and disease-associated pathogenic DNA variants could possibly be repaired, preventing genetic disorders in rare cases where both parents are homozygous for a recessive genetic disorder (e.g. cystic fibrosis) or when one parent is homozygous for a dominant genetic disorder (such as Huntington's disease) [38-40]. Besides the current safety concerns, that prohibit implementation as of today, ethical concerns arise since the genetic changes that are introduced in germ cells or embryos

may be passed on to future generations. The scientific community has stressed that open discussions with society about this subject are necessary, because along with the potential to prevent disease and suffering, the implementation of GGE may consequences for society as a whole [41-43]. Moreover, clarifying the arguments and values concerning the clinical and ethical use of evolving technologies such as GGE are necessary to build a framework to guide responsible implementation.

Somatic gene editing, a possible treatment option

Developments in somatic gene editing (SGE) - as a (postnatal) therapy for patients with a genetic disorder - are promising, as has been shown for thalassaemia and sickle cell disease [44]. The DNA edits are made in somatic cells after the birth of an affected child and will not be passed on to future generations [45]. The possible (future) availability of SGE as a treatment option, as well as other improvements in (gene) therapy, might impact high-risk couples' reproductive decision-making; for example, possibly less people would opt for reproductive technologies such as PGT or PND, when a successful therapy is available. Consideration of SGE is therefore also included in this thesis.

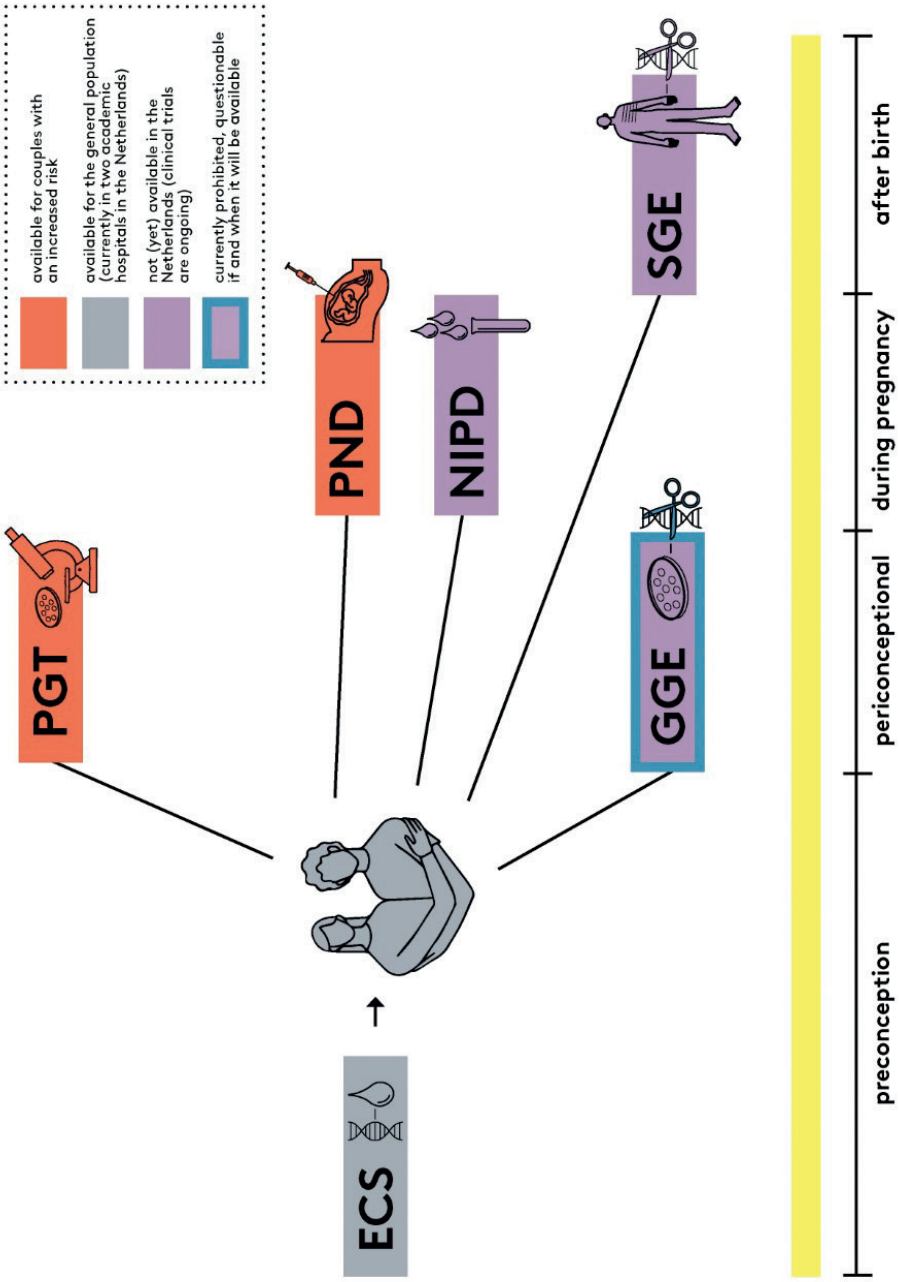

Figure 1. Genetic technologies in the context of reproduction

Possible shifts between technologies

The fields of reproductive medicine and genetics are increasingly connected: it is expected that the technologies will mutually influence each other [46] (Figure 1). For example; when more people undergo ECS, the need and uptake of PND, NIPD and PGT will increase. Or when new technologies are introduced, existing technologies could become unnecessary. For instance, with the introduction and refinement of NIPD, current available PND may become obsolete. Technologies could also converge, for example with NIPT and NIPD, since the same sample of maternal plasma containing cell-free fetal DNA can be used for both screening for aneuploidies and the detection of monogenic genetic disorders.

The broadening scope and issues at stake

Reproductive medicine and genetic technologies are evolving rapidly. The developments of new technologies must be accompanied by discussions on responsible implementation [47], since it is expected that these technologies will alter the landscape of reproductive healthcare and impact generations to come (i.e. with DNA modifications to the germline, such as with GGE), which has implications for society as a whole [41]. Inquiries into the public opinion on emerging technologies can guide further development, elucidate ethical issues and identify best practices. Insights into the public's perspective will also be valuable because the scope of technologies will continue to broaden, both in the number of disorders that can be tested for, and in the terms of growing and expanding uptake, which will result in the increasing utilization of reproductive genetic technologies not only by people who are familiar with genetic disorders, but also by people who have no prior knowledge or experience with genetic disorders. Moreover, another factor that could increase the use and uptake of those technologies among the general public is the growing awareness of genetics and inherited risk factors. This is also influencing the uptake and dependence on genetic technologies around pregnancy, often referred to as the medicalization of pregnancy [48-50]. The growing number of reproductive options and information gained from increased screening and testing poses challenges not only for counselling practices, but has unknown impacts on the couples' decision-making process that warrants investigation.

Stakeholders involved

The developments in reproductive and genetic healthcare come with great opportunities and also potential risks, stakeholders involved have to assure responsible implementation. Therefore, this thesis investigates and presents the perspectives of a broad range of stakeholders to contribute to an acceptable

and successful implementation of the new technologies. The Network of Actors model is used to identify relevant stakeholder groups [51]. Stakeholders including health professionals, scientists, ethicists, policy makers, couples, patients and the general public were actively engaged. According to the Network of Actors model described by Achterbergh et al. [52], a condition for responsible and successful implementation of technologies in healthcare is that stakeholders attune their roles and responsibilities. One group of stakeholders, the scientists and researchers, develop new *technology*. Furthermore, citizens, patients and/or the target population may have a *demand* before a technology will be used or is considered acceptable. The governmental and advisory agencies develop policy and draft regulations for technologies and also define the *acceptability* of new technologies. Lastly, the implementation of new technologies requires an adaptation and *organisation* of the healthcare professionals working in the field who support and guide it. Correspondingly, before change, or implementation, can take place responsibly, all actors need to be considered. Roles and responsibilities should possibly be reallocated in the process [52] (Figure 2).

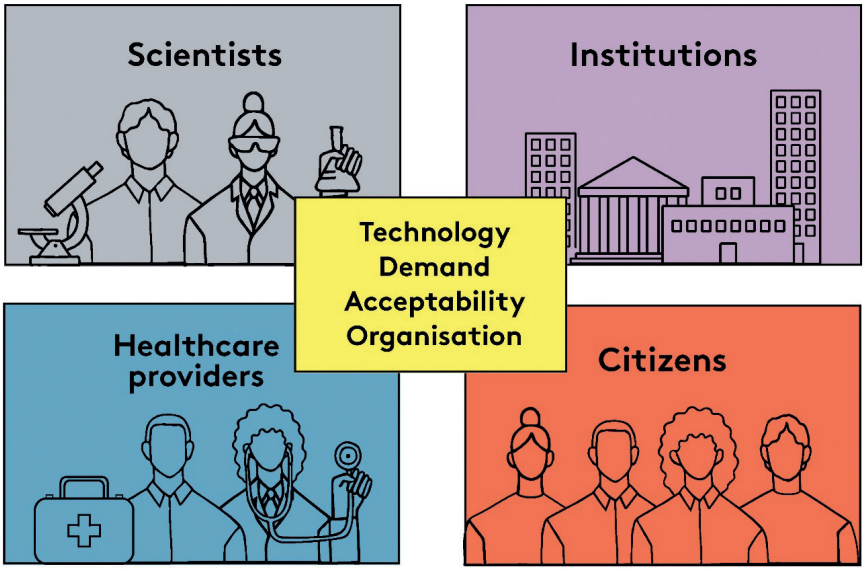

Figure 2. Stakeholders involved with the reproductive genetic technologies, based on the Network of Actors model [51, 52]

Aim and research questions of this thesis

The aim of this thesis is to gain more insight into the perspectives of a broad variety of stakeholders on the development, desirability, (further) implementation and expected dynamics of current and possible future reproductive genetic technologies. These insights are expected to elucidate the demands, concerns, support and expectations of stakeholders in order to contribute to responsible implementation.

New reproductive genetic technologies are addressed: ECS, NIPD, GGE, and the possible treatment option of SGE, all of which are in different stages of development and implementation. These are considered in relation to already existing technologies (PGT and PND).

Research questions

1 What are the views of couples who have an increased risk of having affected offspring with a genetic disorder on both currently available and future reproductive genetic technologies, and how does this impact reproductive decision-making? **(desirability and demand)** *(chapter 2, 3 and 4)*
2 What are the attitudes and experiences of the general population concerning new reproductive genetic technologies? **(desirability and support)** *(chapter 3, 4 and 5)*
3 What are the published reasons in favour of and against the clinical application of a possible future reproductive genetic technology **(such as germline genome editing? (arguments and values)** *(chapter 6)*
4 What are the views and expectations of experts working in the field of reproductive and genetic medicine regarding new reproductive genetic technologies? **(acceptability and support)** *(chapter 7)*

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"Everything changes, everything moves, everything resolves,
everything flies and goes away."

- Frida Kahlo

CHAPTER 2

How will new genetic technologies, such as gene editing, change reproductive decision-making? Views of high-risk couples

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Abstract

Couples at increased risk of having offspring with a specific genetic disorder who want to avoid having an affected child have several reproductive options including prenatal diagnosis (PND) and preimplantation genetic testing (PGT). In the future, non-invasive prenatal diagnosis (NIPD), germline gene editing (GGE) and somatic gene editing (SGE) might become available. This study explores if, and how, availability of new genetic technologies, including NIPD, GGE, SGE, would change reproductive decision-making of high-risk couples. In 2018, semi-structured interviews were conducted with 25 genetically at-risk couples. Couples previously had received genetic counselling for PND and PGT, and in most cases opted for (one of) these techniques, at one Dutch Clinical Genetics Center between 2013-2017. Considerations participants mentioned regarding the hypothetical use of NIPD, GGE and SGE, seem similar to considerations regarding PND and PGT and are reflected in underlying concepts. These include safety and burden for mother and child, and moral considerations. Couples generally favoured NIPD over PND as this would be safe and enables earlier diagnosis. Increased opportunities of having a 'healthy' embryo and less embryo disposal were considerations in favour of GGE. Some regarded GGE as unsafe and feared slippery slope scenarios. Couples were least favourable towards SGE compared to choosing for a genetic reproductive technology, because of the perceived burden for the affected offspring. With the possibly growing number of technological options, understanding high risk couples' perspectives can assist in navigating the reproductive decision-making process. Counsellors should be prepared to counsel on more and complex reproductive options.

Introduction

Currently there are two main reproductive options available to couples facing an increased risk of having offspring with a specific genetic disorder and who wish to avoid having an affected child: invasive prenatal diagnosis (PND) (chorionic villus sampling or amniocentesis), possibly followed by termination of pregnancy if the fetus is affected, and preimplantation genetic testing (PGT). PGT involves intracytoplasmic sperm injection (ICSI), genetic testing and transfer of unaffected embryos with a strongly reduced chance of having to consider pregnancy termination, but requires an intense treatment process [1]. In addition, when pregnancy is achieved after PGT, couples are generally still offered PND because of the low risk of misdiagnosis. Other reproductive options are: refraining from having (more) children, using donor sperm or donor oocytes, considering adoption, or accepting the risk. Reproductive decision-making for high-risk couples is complex and known to be influenced by several factors, including the severity of the condition [2-6], experiences with the condition [1-4, 6, 7], having an affected child [3, 5, 8], attitudes towards pregnancy termination [1, 6-8], the desire to have genetically-related children [1, 8], and perceptions on new technologies and their characteristics (e.g. safety) [1, 3, 6, 7].

In recent years, genetic technologies have developed rapidly. One new reproductive genetic technology is non-invasive prenatal diagnosis (NIPD) using cell-free placental DNA. NIPD nowadays is increasingly available for the detection of monogenic disorders, for example cystic fibrosis (CF) [9]. Challenges in performing the procedure and the costs involved, however, still limits its application [10]. Compared to PND, NIPD can be performed earlier in pregnancy, at around 8 weeks gestational age, and has no procedure-related miscarriage risk [10]. However, if the NIPD result shows that the fetus is affected, the couple is nevertheless confronted with a decision regarding continuing the pregnancy or not and in some cases invasive diagnostic confirmation is recommended [11].

Another, not yet available, possible future reproductive technology is germline gene editing (GGE). Targeted DNA changes could be performed in either immature oocytes and sperm or in early stage embryos, hereby 'repairing' the known disease-causing variant [12]. Although some people argue that PGT is sufficient to fulfil the wish to have an unaffected child, there are cases where GGE is the only option for conceiving genetically-related non-affected offspring, for example when both partners have CF [13]. GGE is a heavily debated technology. Due to experiments without regulatory oversight, the call for a broad societal debate on the socio-ethical and legal implications of GGE has intensified [14]. Besides GGE, developments in somatic gene editing (SGE), as a therapy

for patients, are promising, as has been shown for thalassemia and sickle cell disease [15, 16]. SGE is considered less controversial than GGE since the DNA edits are made in somatic cells after the birth of an affected child and will not be passed on to future generations. The possible (future) availability of SGE as a treatment option, as well as other improvements in therapy, might change the need for current reproductive technologies [17].

It is not yet clear whether, and how, the developments in new reproductive technologies such as NIPD and GGE will influence couples' reproductive decisions. On the one hand, new reproductive options might increase autonomy for genetically at-risk couples, while on the other hand, these developments could also complicate the already complex decision-making process and it could be more difficult to make an informed decision [18]. Concerns about the rapid introduction of new emerging reproductive genetic technologies in clinical practice are being raised by experts [13, 19], and little is known about how high-risk couples would perceive these new options. It is important to explore high-risk couples' perspectives alongside the technical developments, as these couples might represent the possible future users [20]. Couples' perspectives can inform policy-making and in response to their needs, genetic counselling can be adjusted. This study explores the views and considerations of genetically high-risk couples for opting for or against the (possible) future available techniques NIPD and GGE, in relation to their current reproductive decisions. Additionally, the potential influence of the availability of SGE on couples' reproductive decision-making is explored.

Materials and Methods

A qualitative semi-structured interview study with both or one partner of couples at high risk of having affected offspring with a genetic condition was conducted. Approval was obtained from the medical ethical committee of the Amsterdam University Medical Centers, location Academic Medical Center (AMC) (W18_054).

Participants and recruitment

Purposive sampling was used. Sixty-three out of 556 high-risk couples that had been referred to the Department of Clinical Genetics of AMC for genetic counselling about PGT and PND between 2013 and 2017, were invited. AMC is one of four centres in the Netherlands that offers genetic counselling on PGT. Throughout the article the term PGT is used for both PGT-M (Monogenic) and PGT-SR (Structural Rearrangements). Couples attending these counselling sessions come from different regions in the Netherlands, mostly from the Western

provinces. Couples were invited for the study via both email and regular mail by two clinical geneticists [P.L. and I.M.]. A total of 25 interviews (with a total of 35 participants; ten couples and fifteen individuals belonging to a couple) were conducted (response rate 40% (25/63)). Reasons for non-participation were not investigated. To include a range of couples, the selection was based on different inheritance patterns (autosomal dominant, autosomal recessive, X-linked or chromosomal imbalance) and having an affected child or not. The selected couples had received genetic counselling by five different counsellors in the AMC.

Procedure and interview guide

The interviews, lasted around 45 minutes. Of the 25 interviews, 18 were conducted face-to-face and seven by telephone between April 2018 and July 2018. One researcher [I.D], experienced in qualitative research and who had not been involved in the previous genetic counselling of the couples, conducted all the interviews. All participants signed informed consent. An interview guide was developed by the research team consisting of a clinical geneticist, an embryologist, and two health scientists. The first part of the interview focused on factors that influenced reproductive decisions previously made. In the second part, the new (future) reproductive technologies NIPD and GGE were introduced and briefly explained by the interviewer, as well as SGE as a possible future available therapy (see Supplementary Appendix 1). It was explained that NIPD is the most developed technology. In addition, GGE and SGE were explained as possible future (reproductive) genetic techniques in a hypothetical way.

Data analysis

The interviews were audio-recorded and transcribed verbatim. For reporting and analysing qualitative data we adhered to the 32-item COREQ checklist [21]. Thematic content analysis with open coding and interviewing was performed simultaneously [22]. Interviewing stopped when data saturation was reached, i.e. no new themes were generated. For the analyses, the transcripts were read multiple times to get familiar with the data and to enhance validity. Six interviews were independently coded by L.H. and I.D. to increase reliability; all other transcripts were coded by I.D. In an iterative process, the codes were grouped into relevant themes and clustered into categories related to the research question. A preliminary codebook was drafted deductively and adjusted after the first transcripts were coded. The final codebook was established to ensure efficient analysis. Findings were discussed with three researchers [I.D.,L.H.,P.L.] until consensus was reached. ATLAS.ti. software was used to manage the data and

coding process. Quotes were translated from Dutch to English to illustrate the themes.

Results

Participants' characteristics and reproductive decisions are summarized in Table 1. Of the 25 couples, six couples had refrained from PGT. Of the 19 couples that opted for PGT, five couples were still going through the PGT treatment process, while four couples had already completed the process and ten couples had stopped because of a spontaneous pregnancy or other reasons. Fourteen couples had opted for PND. Five couples had children that were affected with the genetic condition and/or were deceased. Four of the six participants who were a carrier of an autosomal dominant disorder suffered from symptoms of the condition themselves (Supplementary Table S1).
The findings from the interviews are structured according to: (1) Couples' previous considerations for opting for or refraining from PND and/or PGT; and (2) Perspectives on new reproductive technologies (NIPD, GGE) and SGE. Themes and representative quotes are presented in Tables 2 and 3, respectively.

Table 1. Characteristics of participants, n=35

Characteristics	
Gender, n (%) Female Male	24 (68.6) 11 (31.4)
Interviews, n (%)[a] Couples (woman and man present) Individuals	10 (40.0) 15 (60.0)
Mean age in years (SD) [range]	33.2 (3.89) [27 – 40]
Dutch background, n (%)[b]	33 (94.3)
Education, n (%)[c] Low Intermediate High	- 9 (25.7) 26 (74.3)
Religious, n (%)[d]	6 (17.1)
Type of inheritance of condition at-risk, n (%)[e] AD AR XLR/D Chromosomal imbalance	6 (24.0) 5 (20.0) 12 (48.0) 2 (8.0)

Table 1. Characteristics of participants, n=35 *Continued*

Characteristics	
Mean time between reproductive genetic counselling and interview in years (SD) [range]	3.4 (1.42) [1.0- 6.0]

[a] 25 interviews were conducted with a total of 35 participants, of which 10 were with couples and 15. were with individuals (belonging to an invited couple). Of the interviews with individuals, one was with a male and the others were with female participants.

[b] One participant was from India and one was from Spain.

[c] Low: primary school, lower level of secondary school, lower vocational training. Intermediate: higher level of secondary school, intermediate vocational training, High: high vocational training, university.

[d] Five participants considered themselves Christian but were not (or hardly) practicing and one participant was of another denomination.

[e] AD, Autosomal Dominant: Andersen-Tawil syndrome, Gorlin syndrome, Hereditary breast and ovarian cancer (n=2), Hereditary diffuse gastric cancer, Huntington's disease. AR, Autosomal Recessive: Cystic Fibrosis, Usher syndrome, Pontocerebellar hypoplasia type 2, Congenital Disorder of Glycosylation type 1a, Non-ketotic hyperglycinemia. XLR, X-Linked (Recessive): Adrenoleukodystrophy, Becker Muscular Dystrophy, Chronic Granulomatous Disease, Desmyopathy, Duchenne muscular dystrophy, Fabry disease, Hemophilia, Ornithine Transcarbamoylase Deficiency, Pelizaeus-Merzbacher disease. XLD, X-Linked (Dominant): Fragile X syndrome (n=3). Chromosomal imbalance: Reciprocal translocation and Inversion chromosome.

Previous considerations for opting for or refraining from PND and/or PGT

Participants who initially opted for PND and/or PGT were all couples who chose these techniques because they preferred to avoid the birth of an affected child. They described their former process of reproductive decision-making as intense, complex and iterative. The initial reproductive option of choice was quite often not in concordance with the actual performed reproductive option, in particular regarding PGT (see Supplementary Table S1). For example, couples discontinued the (planned) PGT procedure because they had an (unexpected) spontaneous conception during the PGT preparation process, leaving PND as the only available option besides accepting the risk.

Table 2. Couples' considerations for and against PND and/or PGT illustrated with representative quotes

Theme	Representative quote	Quote #
Safety for the unborn child and mother	"She [the counsellor] said that the risk of another miscarriage was too high and besides that, it's not really pleasant for yourself as well [PND, invasive testing] [...] So, I thought that was very scary and I was anxious about the test result." [Couple, AR, #8]	1.1
	"I thought it was a horrible idea for such an instrument [needle with invasive testing] to be so close to my child. That is of course not very pleasant." [Woman, XLR, #20]	1.2
Success rate and burden of the technique	"Yes, you will appear on the waiting list and then it would only be our turn somewhere mid-July. I think [PGT] is one big frustrating process. I cannot say otherwise." [Man, AD, #2]	1.3
	"I always remember one comment, she [the counsellor] said: 'Yes 30%, that's of course not very much [for a pregnancy with PGT], but if you can win the lottery with 30% you would buy a lot of tickets'. Then I thought: yes, you can also see it that way..." [Woman, XLD, #21]	1.4
Decision-making regarding pregnancy termination	"Back then [previous pregnancy] we still had hope: it [fetus] is staying in the womb, but is it OK? You don't dare to become attached to it. This time we wanted to avoid this [opted for PGT]." [Woman, chromosomal imbalance, #24]	1.5
	"I find it very difficult anyway, because if you are, after all, pregnant and then you hear: "Well, your child has a disorder," then you have to make the decision: terminate yes or no. I think I will find that very, very, difficult" [Man, chromosomal imbalance, #25]	1.6
Preference for a natural pregnancy	"It's simply no fun to make children this way [PGT]. Of course, it's not only about the sexual intercourse, but just the whole thing that you are not procreating naturally." [Man, AD, #2]	1.7
Personal experiences with the genetic condition	"Well, that [PND] was not an option for us. Because I am here as well, you know." [Woman affected with disorder, AD, #1]	1.8
	"That [opting for any technology; PND or PGT] would almost feel like a betrayal of my [affected] son; the one that I already have." [Couple, AR, #9]	1.9

Abbreviations: AD, Autosomal Dominant; AR, Autosomal Recessive; PND, Prenatal Diagnosis; PGT, Preimplantation Genetic Testing; XLD, X- Linked (Dominant); XLR, X- Linked (Recessive).

Frequently mentioned considerations that influenced the decision regarding PND and/or PGT were: safety for the unborn child and mother because of the invasiveness of the procedure and fear for the procedure-related miscarriage risk with PND (Table 2, quote 1.1 and 1.2), the burden of the procedure and success rate of the technique, mostly mentioned in the context of PGT (quote 1.3 and 1.4), decision-making regarding pregnancy termination (quote 1.5 and 1.6), and the preference for a natural pregnancy (quote 1.7). Overarching factors, not necessarily related to the technologies, that influenced couples' reproductive decision making were perceived severity and personal experiences with the disorder, such as having the condition themselves (in case of an autosomal dominant disorder) or having an affected child (quote 1.8. and 1.9).

Perspectives on new (reproductive) genetic technologies

Considerations regarding NIPD, GGE and SGE were discussed in comparison to the available reproductive genetic technologies (PND and PGT) (Table 3). Generally, participants emphasized that they would only consider these new technologies if safety requirements are met, side effects are minimized, and success rates have been proven. The considerations in favour of and against these new technologies are summarized in Table 4.

Views towards NIPD

Safety for the unborn child and mother

If it would be possible to safely use NIPD for monogenic disorders, the responses of participants were generally positive. Participants considered the non-invasive component as the most appreciated characteristic of NIPD compared to PND (Table 3: quote 2.1). Some couples would want to use NIPD to be prepared and informed about the health of the unborn child instead of considering a pregnancy termination (quote 2.2).

Earlier diagnosis and decision-making regarding pregnancy termination

A diagnosis at an earlier gestational age was considered as an important advantage of NIPD compared to PND. A majority of the participants argued that the longer they are pregnant the more attached they become to the unborn child and termination becomes more difficult. Moreover, an earlier result would enable termination of pregnancy by curettage, instead of an induced early labour procedure, which was considered less traumatic (quote 2.3).

Table 3. Couples' perspectives on new (reproductive) technologies (NIPD, GGE and SGE) in relation to the existing reproductive options of PND and PGT: representative quotes by theme

Theme	Representative quote	Quote #
Perspectives on NIPD		
Safety for the unborn child and mother	"... non-invasive, that sounds like music to our ears. You know that if you go into that amniotic sac and you are there where the baby is, you have a chance, yes, of infection, you name it. Yes [NIPD] always sounds better [than invasive testing]." [Woman, XLR, #19]	2.1
	"But when I look back, I think I had... yes, I think I had used it [NIPD], more to just be informed and that then, yes, you can already adjust to that news or something. Even if you do nothing with it [termination of pregnancy]." [Couple, AR, #7]	2.2
Earlier diagnosis and decision-making regarding termination of pregnancy	"... time is really everything. Of course, if you then terminate [after PND result], what do you terminate and at what stage is that [the fetus]. The curettage instead of giving birth makes a huge difference, but the number of weeks of waiting is...normally you tell people after 10-12 weeks that you are pregnant, if you already have the test result it is nice. Now, you have to stay quiet, but at a certain point it becomes physically complicated to do that." [Women, XLD, #22]	2.3
Views towards NIPD compared to PGT	"I would not do that [terminate a pregnancy] for the reason that this gene would be in it, because if you have it [the mutation] that does not mean that you will be severely ill. There's just a sensitivity to that cancer. And that means, yes, I can also live to be a hundred years old, because they got there early enough. But then yes, no, terminating a pregnancy is ethically crossing a line for me, availability of NIPD would not change the choice for PGT for me for this reason" [Women AD, # 1]	2.4
	"We have experienced through PGT that our number of affected embryos was so incredibly high. So I don't know if I would dare [opt for NIPD]. I do think for us, PGT was a very safe way. Yes, of course, you would rather not terminate a pregnancy." [Man, AD, #2]	2.5

Table 3. Couples' perspectives on new (reproductive) technologies (NIPD, GGE and SGE) in relation to the existing reproductive options of PND and PGT: representative quotes by theme Continued

Theme	Representative quote	Quote #
Perspectives on GGE		
Safety concerns	"I would opt for PGT, because I have more faith in this, than to fix something [with GGE]. My car is sometimes repaired and it doesn't always come back in good shape." [Woman, XLR, #20]	3.1
More unaffected embryos and no embryo disposal compared to PGT	"But of course there are [more options] and certainly if you have multiple abnormalities. I mean, the more abnormalities, or chance of a disease, the nicer it is to cut and paste it a little, until its correct." [Woman, XLD, #21]	3.2
	"Suppose it [GGE] is safe and the consequence is that you do not have to throw away embryos, so that you can have many more embryos from one puncture [...] I have no moral objections to that. Surely it's only beautiful if your child is not burdened with such an awful disease?" [Man, AD, #4]	3.3
Slippery slope scenarios and unnatural	"On the one hand, I find it [GGE] very scary, because you are messing with nature so much. But it would be great if it could be done like this. My gut feeling is that I'm against modifying DNA. If you could modify DNA, how far do you go? That's also the ongoing discussion now [...] You can choose your baby in a catalogue. I want red hair with freckles, white skin, very nice. A gene for breast cancer that can be detected very early, will you take it out or not? But glasses, yes, how bad are glasses?" [Woman, XLR, #15]	3.4
	"We are not religious or anything like that, but as far as I'm concerned [...] I think with this you're going a bit too far in human creation. Then you really intervene in the structure of the DNA, you intervene with nature." [Woman, XLR, #19]	3.5

Table 3. Couples' perspectives on new (reproductive) technologies (NIPD, GGE and SGE) in relation to the existing reproductive options of PND and PGT: representative quotes by theme Continued

Theme	Representative quote	Quote #
Costs and fears for inequality	"We can end up in such a world, that such differences are created, some can afford it [GGE] and others cannot. I don't think that's desirable." [Man, AD, #2]	3.6
	"To fix it, let's be honest, if you have sick children it costs society a lot of money. I see what our son with his illness costs with his illness [...] It would be better for society if you could just bring healthy children into the world. It sounds a bit harsh [...] If you know that you have a certain chance of having a sick child, I would say fix it." [Woman, XLR, #20]	3.7
Perspectives on SGE		
Burden for the future child	"If you look at the options, then this [SGE] is the least interesting, because you are messing with a child that is still so small. They are still so vulnerable; I think that is difficult to watch. Look, what happens to me is not interesting, I don't really care because I know what I do it for. But such a small person has no clue." [Couple, AR, #8]	4.1
	"I think, let's have all the fuss in advance. That will be on our account, the child is not bothered by it then [...]. Of course it also depends on whether it all succeeds or not, or whether a complication occurs, and so on." [Woman, AD, #3]	4.2
	"The advantage is a natural pregnancy, but I would also find it [SGE] very intense if such a small baby had to undergo enormously intense surgeries and that you know this beforehand..." [Couple, AR, #10]	4.3

Table 3. Couples' perspectives on new (reproductive) technologies (NIPD, GGE and SGE) in relation to the existing reproductive options of PND and PGT: representative quotes by theme Continued

Theme	Representative quote	Quote #
Possibility of a natural pregnancy	"There were no issues in terms of fertility, so yes, the option of getting pregnant naturally is there [can opt for SGE], which I thought was a much nicer idea, but there is this risk [of having an affected child]..."[Woman, AD, #1]	4.4
	"Yes, because it [PGT] is a very heavy process. With this [SGE] you can get pregnant naturally. So yes, that sounds a lot easier to me... yes but what about the certainty [of SGE]?" [Woman XLR, #13]	4.5
	"Suppose you have completed the pregnancy, you have already furnished your house for the baby and then, the treatment would go wrong after all, then you already have that entire process of the entire pregnancy and gave birth and if you then have to say goodbye to your child, because that treatment does not work out well, that is terrible, I would opt for something else instead." [Woman, chromosomal imbalance, #24]	4.6
Difficult to anticipate	"I don't know, it's [SGE] still very unknown. I have no idea, I find it hard. If your child is sick and it can be treated, everyone would opt for that. Even though it would take five surgeries until your child is healthy you would do it. Because you want your child to go through life without worries." [Woman, XLR, #20]	4.7

Abbreviations: AD, Autosomal Dominant; AR, Autosomal Recessive; GGE, Germline Genome Editing; PND, Prenatal Diagnosis; NIPD, Non-invasive Prenatal Diagnosis; PGT, Preimplantation Genetic Testing; SGE, Somatic Genome Editing; XLD, X- Linked (Dominant); XLR, X-Linked (Recessive).

Views towards NIPD compared to PGT
Participants discussed NIPD in relation to PGT. Couples who wanted to avoid a possible decision regarding pregnancy termination would prefer PGT over either NIPD or PND. Terminating a pregnancy for a condition you suffer from yourself was considered a difficult decision by participants as illustrated in quotes 2.4 and 2.5. Some couples mentioned that they would prefer NIPD instead of PND during the PGT process, for confirmation of PGT results.

Views towards GGE

Safety concerns
Overall participants seemed positive of the idea of GGE, but some were hesitant due to safety issue and side effects. They had more trust in PGT and mentioned that with GGE there was a chance that the induced DNA changes might have unintended consequences (quote 3.1), for example making the cut at the wrong place (known as off-target effects).

More unaffected embryos and no embryo disposal compared to PGT
The possibility of "repairing" affected embryos by GGE besides only selecting unaffected ones by PGT, was mentioned by participants as an opportunity to increase their chance of getting pregnant with an unaffected child, which was considered as a great advantage of GGE (quote 3.2). In addition, participants argued that women would have less unpleasant ovum pick-up procedures to undergo. Furthermore, discarding of embryos was mentioned by many participants as a negative aspect of PGT because of the moral status of embryos in general (quote 3.3). A few participants argued that with PGT their children might have to face the same reproductive dilemmas because, in their specific situation, the transferred embryos could be healthy carriers of the same disorder (e.g. selecting female embryos in X-linked disorders), which was another argument in favour of GGE.

Slippery slope scenarios and unnatural
Some participants feared that once GGE is allowed for treating severe genetic conditions in the embryonic stage, it would also be allowed for other goals, like enhancement purposes such as cosmetic changes and increased intelligence (quote 3.4). For some, gene editing of embryos was unnatural and interfering in the DNA is a line that should not be crossed (quote 3.5).
Costs and fears for inequality

Fears of abuse of the technology for the purpose of earning money or ambiguous indications were expressed. On the one hand concerns were voiced that only rich people would be able to afford GGE if health insurances would not reimburse it, giving rise to inequality issues (quote 3.6). On the other hand, participants mentioned that one of the expected benefits of GGE would be that repairing embryos might be cost-saving compared to destroying affected embryos (quote 3.7).

Views towards SGE as a therapeutic option

Burden for the future child

Participants preferred to put the burden for decision making, for example undergoing the PGT-process, on themselves over putting their child at risk for a possible available treatment (SGE). This resulted in a great reluctance regarding SGE (quote 4.1 and 4.2). Participants who were identified as a high-risk couple after the birth of an affected child, were more positive about SGE, but would not opt for SGE initially over other reproductive options because they expected it to be an intense burden for their future child (quote 4.3). Nevertheless, it reassured participants that there would be a treatment available if the PGT or PND test results turned out to be false negative. SGE was therefore viewed as a kind of "safety net".

Possibility of a natural pregnancy

Once SGE would be proven safe and successful, some participants stated that they might opt for SGE and refrain from PND or PGT at all. Participants who preferred a natural pregnancy, with natural conception, and who therefore refrained from PGT, were generally more positive about SGE (quote 4.4 and 4.5) but also still cautious, as they feared that the therapy might not be successful (quote 4.6).

Table 4. Considerations regarding the new technologies from the participants' perspectives in terms of underlying concepts

Considerations *in favour* of the new technologies				
	Safety (for mother and child)	**Burden (for mother and child)**	**Moral considerations**	**Natural pregnancy**
NIPD	Safe for the unborn child (compared to PND)	Less inconvenient for the mother (compared to PND)	Earlier testing (compared to PND): 1] Less time to become attached to the unborn child results in a less emotional decision regarding possible termination of pregnancy 2] Increased possibility of a medical abortion versus surgical or induced abortion procedure	Like in PND, with NIPD a natural pregnancy is a possibility which is experienced as a positive aspect compared with PGT
GGE		More possibilities – due to editing – of having unaffected embryos resulting in possibly less oocyte punctures (compared to PGT)	- No embryo disposal (compared to PGT) - Repairing embryos could save costs for individuals and society	
SGE		Having a 'care-free' pregnancy: no testing, no anxiety waiting for test results	When you (unexpectedly) have an affected child, this technique could offer a potential treatment for the child	Possibility of having a natural pregnancy without medical interventions (compared to PGT)

Table 4. Considerations regarding the new technologies from the participants' perspectives in terms of underlying concepts *Continued*

Considerations *against* the new technologies				
	Safety (for mother and child)	**Burden (for mother and child)**	**Moral considerations**	**Natural pregnancy**
NIPD			If one wants to avoid an affected child, termination of pregnancy is still the only option which could be difficult when you morally object to termination	
GGE	Safety issues in terms of side effects and unintended consequences (compared to PGT)		-Risk of slippery slope scenarios: how to decide on indications and how far do we go as a society? - Fear for inequality in access - Procedure is considered unnatural: 'crossing a line', modifying human DNA	
SGE	Safety concerns for the future child	'Treatment' burden for the future child (let parents carry the burden of reproductive technologies instead of the future child)	Prevention is better than cure (in order to make difficult decisions beforehand)	

Abbreviations: GGE, Germline Genome Editing; NIPD, Non-invasive Prenatal Diagnosis; PGT, Preimplantation Genetic Testing; PND, Prenatal Diagnosis; SGE, Somatic Genome Editing.

Difficult to anticipate

Most participants experienced a difficulty in forming a realistic opinion on SGE. Many found thinking in a hypothetical way about SGE as a future therapeutic option, without clear clinical examples, difficult to imagine (quote 4.7). Moreover, it could also feel like taking a risk because there is no information so far about the chance of treatment success. For this reason and for the possible burden on the future child several participants considered SGE the least favourable option to anticipate on.

Discussion

This study explored the views of genetically high-risk couples, who previously received PND/PGT, on NIPD, GGE and SGE in relation to the reproductive decisions they had previously made. Considerations participants mentioned regarding the hypothetical use of NIPD, GGE and SGE seem similar to considerations regarding PND and PGT and are reflected in underlying concepts, summarized in Table 4. These concerned the safety aspects and burden of the specific technologies, moral considerations such as attitudes towards the status of the embryo and pregnancy termination and the preference for a natural pregnancy.

As was shown in previous studies [18], participants were positive about NIPD because they considered it safer for mother and child and it enables earlier testing compared to PND. Therefore, a shift from current invasive prenatal methods to NIPD might possibly occur in the Netherlands. A negative attitude towards termination of pregnancy, however, was a reason to refrain from NIPD and to (still) opt for PGT as was shown previously [6], despite the favourable characteristics of NIPD. Some couples expressed negative attitudes towards pregnancy termination, but indicated that they would nevertheless opt for NIPD just to be informed and prepare for a child with a genetic condition, as was shown earlier for NIPD for CF [23] and non-invasive prenatal testing for Down syndrome [24]. Participants in our study expressed their views on NIPD in a different manner compared to experts as described in the literature. Experts generally emphasize technical aspects, as the labour-intensity and accuracy of NIPD [25], whereas participants from our study emphasized the attitudes towards pregnancy termination, earlier diagnosis, and the value of a natural pregnancy as important factors for consideration. It is needless to say that both valued safer diagnosis. Concerns of routinisation and informed consent were not expressed by participants, in contrast to a qualitative study in the United Kingdom (UK) with carriers of recessive disorders [26], in which issues around consent were explicitly addressed. Furthermore in the UK, in contrast to the

situation in the Netherlands at the time of the interviews, NIPD is available in a growing number of hospitals, and favoured by high-risk couples [23], however challenges regarding costs remain [27]. GGE was considered generally positive because, according to participants, it would offer increased possibilities compared with PGT since more embryos, either unaffected or treated embryos, could be transferred and less embryos disposed [1], as previously stated by experts [19, 28]. In this way less IVF/ICSI cycles are needed, which could decrease burden for the mother. These findings are similar to previous studies assessing people's perspectives [29, 30]. However, fears of the technology being abused were expressed. Couples reported concerns about the responsible use of GGE; it should be used only for serious conditions and not to create 'designer babies', as was shown by others [13, 19]. In the literature, it has been argued that availability of GGE might lead to discrimination of people who live with disabilities, as was discussed earlier for other selective reproductive technologies [31]. Changing the DNA of embryos was considered "a bridge too far" by some of the participants and therefore they would prefer the established PGT technology. Even though participants had concerns, they seemed generally more positive towards GGE than the general public, possibly because they reason from an experiential perspective [32]. However, a lack of in-depth understanding on the implications of genome editing (somatic as well as germline) could have biased participants' views as the ability to provide arguments partly depends on prior knowledge [33].

Couples generally considered NIPD and GGE as options to anticipate on, provided these are safe, effective and available. Participants generally viewed taking the risk by conceiving naturally and treating an affected child after birth with SGE as the least favourable option to consider before pregnancy. Moreover, couples were uncertain about what SGE might look like clinically. This finding is in line with a US focus group and survey study that assessed the willingness of sickle cell patients to participate in SGE clinical trials [17]. In contrast to our findings, earlier studies among the general public were more supportive towards clinical use of SGE as opposed to GGE [30, 34]. Explanations for more public support of SGE could be that first, germline edits are inheritable and therefore considered controversial, while SGE could offer a curative treatment for individuals [29]. Second, in public opinion studies SGE was not discussed in relationship to reproductive technologies as in this study, but as a possible therapy. Clinical trials of SGE are ongoing and results are promising according to experts [35]. However, when offering SGE within a range of reproductive options (e.g. PGT or NIPD), participants are reluctant and would rather opt for reproductive options where the burden would be on the couples' shoulders, instead of burdening their child with a treatment.

In addition to perspectives on the technologies explored in this study, other developments in the reproductive field should be taken into account, such as preconception carrier screening for recessive disorders, which may increase reproductive choice [36]. Moreover, trophoblast retrieval from the cervix (TRIC) could potentially detect foetal DNA at an even earlier gestational age compared to NIPD [37].

Study strengths and limitations

This study has several strengths. Firstly, few studies have been conducted on possible future users' views on new technologies such as GGE and SGE [38]. Secondly, a variety of participants were included in terms of inheritance patterns to explore a broad range of perspectives. Limitations of this study are that, first of all participants were recruited from one centre only, which could have resulted in bias because they all received their genetic counselling regarding reproductive decision making in this centre. Moreover, participants mostly came from the Western provinces. As with the regional differences that are known for non-invasive prenatal testing (NIPT) uptake [39], this could influence people's interest in other reproductive technologies and therefore results must be interpreted with caution. Healthcare systems and cultures differ between countries, and the perspectives of couples could as well [39]. Thirdly, only high-risk couples who primarily had expressed (some) interest in PGT, and who were counselled about PGT and PND, were interviewed. Couples who refrained from these options, and/or who refrained from having children in order to avoid an affected child, were not included in our study. Exploring their views will be a next step for research because they could have other perspectives on the technologies. Moreover, views on reproductive decision-making were explored retrospectively, which could have resulted in recall bias. Fourthly, participants were relatively highly educated, which could have biased the results [3]. Furthermore, seven interviews were conducted by telephone which limits body language response. Lastly, since GGE and SGE were explained in hypothetical scenarios, it was hard to elicit real perspectives that reflect the actual reproductive decision-making of the participants.

Conclusion and implications

With the results of this study, bearing in mind that this is a study regarding the hypothetical use of future technologies, we attempted to gain more insight into the future dynamics of the reproductive decision-making process of high-risk couples counselled for PND and/or PGT who want to avoid the birth of an affected child. Understanding these couples' perspectives can assist in navigating reproductive decision-making [7]. Genetic counsellors could bear in mind the concepts underlying decision-making identified in this study, and explore together with couples how they feel about the different options and support them in their decision. The non-invasiveness and earlier gestational diagnosis of NIPD are considered important advantages. Moreover, when comparing PGT to NIPD results suggest that high-risk couples, who previously had made a reproductive decision, and who have objections towards termination of pregnancy will continue to opt for PGT, instead of opting for NIPD. The results may also suggest parallel use of GGE with PGT, if GGE is safe and effective, because of the potential larger number of embryos eligible for transfer. Opting for a natural pregnancy followed by treatment of the child after birth with SGE was evaluated as less positive compared to reproductive options before or during pregnancy, mainly because of the perceived burden for offspring. Though many of the couples' considerations regarding these technologies remain the same in essence, with the growing number of reproductive options, genetic counselling will become more challenging as these new developments will most likely complicate reproductive decision-making. Users' perspectives should be addressed and they should be involved in shared governance and guiding further science and policy-making.

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Supplementary Appendix. Interview guide: explanations of technologies NIPD, GGE, SGE

Introduction

With this interview we want to explore which considerations and experiences are of importance to the reproductive decision-making process with regard to having children and the various options that are available (such as prenatal diagnosis or pre-implantation genetic testing (PGT)), for couples with an increased risk of having an affected child. In addition, I will ask questions on whether the availability of future genetic techniques would influence previous reproductive decision-making. With the results from these interviews, the offer of genetic reproductive technologies and counselling, can be aligned as closely as possible to the wishes and demands of those who use these technologies.

The first part of the interview focuses on the previous reproductive decision-making process of couples. What decision they made and how they have come to those decisions.

New technologies

[Continue interview with new techniques] Interviewer: Besides embryo selection/ preimplantation genetic testing (PGT) and invasive prenatal diagnosis (PND) that we discussed in this interview, I would also like to talk to you about new technologies that are currently being developed. Some of these might become available in the (near) future, while others may never be safe enough to be implemented.

For our study, we would like to know how couples like yourself look at these future technologies and whether or not these technologies would affect couples' reproductive decisions, and why. We would therefore like to know what your views are on the technologies that are currently available and on the new technologies that might become available in the (near) future. Your opinion is very important to us. Little is currently known about what people think of these new technologies. I am going to discuss three new technologies with you in a hypothetical way, emphasizing that none of them are currently available at the moment (in the Netherlands).

Non-invasive prenatal diagnosis (NIPD):

Have you ever heard of non-invasive prenatal diagnosis, also known as NIPD? [If people make the comparison with NIPT for fetal aneuploidy, the differences are explained]. If so, can you tell me what you know about this technique and how you became familiar with it?

Explanation: Suppose that with NIPD, your blood sample could be tested early in pregnancy, to safely and reliably test whether your unborn child has the condition.

Would you prefer to opt for NIPD instead of, for example, chorionic villus sampling? Why (not)? Suppose this method would be offered, would this be an option for you? Would the availability of this technique have influenced your earlier decisions (e.g. regarding PND/PGT)? Why (not)?

Do you have any doubts about this option? If so, can you elaborate?

Germline gene editing (GGE):
Have you ever heard of germline gene editing, also known as embryo modification? If so, can you tell me what you know about this technique and how you became familiar with it?

Explanation: With embryo modification it would be possible to genetically 'repair' the embryo, to ensure that your future child does not have the genetic condition that you are carrying. This technique is currently not available but might be an option in the future. A mutation in the DNA can cause a certain disease. Germ-line gene editing is a technique that would enable medical professionals to repair this mutation in the DNA of the oocytes/sperm or in the embryo. The process of GGE will possibly look similar to PGT.

What do you think about GGE? Can you describe your feelings? Why do you feel this way?

Would you possibly consider this option, if possible? Why (not)?

You have previously (not) opted for PGT – if it would be possible to genetically repair the embryos with the mutation, would you prefer that? Would you possibly consider this? Why (not)?

Do you have any doubts about this technique? If so, can you elaborate?

Somatic gene editing (SGE):
Have you ever heard of somatic gene editing or somatic gene therapy? If so, can you tell me what you know about this technique and how you became familiar with it?

Explanation: With somatic gene editing, body cells are repaired. The cells are removed from the person with the disorder and genetically modified/repaired in the laboratory. Under certain conditions, these cells can be multiplied and returned to the patient via the bloodstream. It might also be possible in the future to introduce the "healthy" or repaired cells directly into the body via an infusion. In this way, genetic conditions can be repaired and treated in the future, soon after birth. This technique is currently not available but might be an option in the future.

What do you think about SGE? Would you possibly consider this? Why (not)?

Do you have any doubts about this technique? If so, what?

Are there any of these techniques (just explained/discussed) that are not acceptable to you? Why? Which of all the techniques would you prefer most? Why?

Do you think that the three options mentioned above (i.e NIPD, germline gene editing or embryo modification and somatic gene editing) should be available for everyone, for certain groups or for no one? Why?

Closing questions interview
Thank you for participating in this research and for your sincerity.

- Do you have any questions at the moment?
- Do you want to add anything else?
- Have I forgotten something?
- Were certain questions difficult or unclear / unpleasant to answer?
- How did you like participating in this interview?

Finally, I will give you a form with a few short questions about your background, would you like to fill this in for me?

Age, education, ethnical background, belief and which conditions occur in your- or your partner's family?

Supplementary Table S1. Characteristics and reproductive decisions of participants (per couple, n=25)

#	Carrier (man/ woman/ couple)	Inheritance	Parents of (n) affected child(ren)	Parents of (n) healthy child(ren)
1.	Woman	AD		1
2.	Man	AD		
3.	Woman	AD		1
4.	Man	AD		1
5.	Man	AD		1
6.	Man	AD		1
7.	Couple	AR	1	1
8.	Couple	AR	1 (deceased within first year)	1
9.	Couple	AR	1	
10.	Couple	AR	1	
11.	Couple	AR	1 (deceased within first year)	2
12	Woman	XLR		
13.	Woman	XLR	1	1
14.	Woman	XLR		1
15.	Woman	XLR		
16.	Woman	XLR		2
17.	Woman	XLR		1
18.	Woman	XLR		1
19.	Woman	XLR		2
20.	Woman	XLR		1
21.	Woman	XLD		1
22.	Woman	XLD		1

	PGT (yes (completeda/ ongoing/stopped)/no)	PND (yes (CVS, AC, FSD)/no)	Planning to have (more) children (yes/ maybe / no/ unknown)
	Yes (completed)	No	Maybe
	Yes (ongoing)	No	Unknown
	Yes (completed)	No	Yes
	Yes (ongoing)	Yes (CVS)	Unknown
	No	Yes (AC)	Yes
	Yes (stopped, due to spontaneous pregnancy)	No	Yes
	No	No	No
	Yes (completed)	Yes (CVS)	Maybe
	No	No	No
	Yes (ongoing)	Yes (AC)	Currently pregnant
	Yes (stopped, due to spontaneous pregnancy)	Yes (2x CVS)	No
	Yes (stopped, relationship ended)	No	Yes
	Yes (stopped, due to spontaneous pregnancy)	Yes (FSD)	No
	No	Yes (CVS)	Maybe
	Yes (ongoing)	No	Currently pregnant
	No	Yes (2x FSD, followed by 1x CVS)	No
	Yes (stopped, due to spontaneous pregnancy)	Yes (FSD)	Yes
	Yes (stopped, did not succeed, a natural pregnancy occurred)	No	Yes
	Yes (stopped due to spontaneous pregnancy)	Yes (2x CVS and 1x AC)	Currently pregnant
	Yes (stopped, due to spontaneous pregnancy)	Yes (FSD and CVS)	No
	Yes (stopped, due to spontaneous pregnancy)	Yes (CVS)	Maybe
	No	Yes (CVS)	Maybe

Supplementary Table S1. Characteristics and reproductive decisions of participants (per couple, n=25) Continued

#	Carrier (man/ woman/ couple)	Inheritance	Parents of (n) affected child(ren)	Parents of (n) healthy child(ren)
23.	Woman	XLD		
24.	Woman	Chromosome imbalance		1
25.	Man	Chromosome imbalance		

[a] Completed: the PGT process resulted in a pregnancy.

AD, Autosomal Dominant; AR, Autosomal Recessive; AC, Amniocentesis; CVS, Chorionic Villus Sampling; FSD, Fetal Sex Determination; PGT, Preimplantation Genetic Testing; PND, Prenatal Diagnosis; XLD, X- Linked Dominant; XLR, X- Linked

	PGT (yes (completed[a]/ ongoing/ stopped)/no)	PND (yes (CVS, AC, FSD)/no)	Planning to have (more) children (yes/ maybe / no/ unknown)
	Yes (ongoing)	No	Maybe
	Yes (completed)	Yes (CVS)	Maybe
	Yes (stopped, did not succeed)	No	Yes

"Erf de ogen van je kind
Kijk er door
Koester je geheime hart tot het eind
Reis ver, drink wijn, denk na
Lach hard, duik diep
Kom terug"

- Spinvis

CHAPTER 3

Preconception expanded carrier screening: a focus group study with relatives of mucopolysaccharidosis type III patients and the general population

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Abstract

Preconception expanded carrier screening (ECS) enables prospective parents to assess their risk of having a child with an autosomal recessive disorder. Knowledge on motivations, feelings and considerations people have towards the offer and use of ECS is limited. To enrich the public and professional discussion on ECS implementation, this study explored the perspectives towards various aspects of ECS in seven focus groups compromising first- and second degree relatives of MPS III patients (N=9, N=4, N=5, N=5) and members of the general Dutch population (N=6, N=7, N=5). The focus groups were audio recorded and the transcripts were qualitatively analyzed to identify themes. Both relatives of MPS III patients and participants from the general population supported offering ECS, in particular for severe, childhood-onset disorders. Important barriers identified for ECS were a lack of genetic knowledge and a perceived lack of personal relevance and awareness, as well as out-of-pocket costs of testing. The majority of participants would prefer full disclosure of individual test results instead of couple-based test results. Moreover, offering people a choice for the way of reporting was proposed. All participants agreed that more efforts, for example by governmental campaigns, should be made to increase awareness on the availability, potentials, and limitations of ECS. Educating prospective parents about ECS is essential for increasing awareness and informed decision making. This study provides valuable insights that can be used by governments and public health authorities when considering implementation of preconception ECS.

Introduction

Preconception carrier screening offers prospective parents the possibility to obtain information about their risk of having a child with an autosomal recessive (AR) or X-linked disorder before pregnancy[1]. Identified high risk couples can consider a range of reproductive options such as preimplantation genetic testing (PGT), prenatal diagnosis, the use of donor gametes, accepting the risk or refrain from having children[2]. Carrier testing for severe genetic disorders is conventionally aimed at couples with an a priori increased risk of having affected offspring based on family history, geographic and/or ethnic background or consanguinity[1-3]. Next-generation sequencing (NGS) allows for testing for multiple AR disorders simultaneously without significantly higher costs, thereby increasing the feasibility of offering universal expanded carrier screening (ECS) panels to the general population[4]. Several commercial companies in the USA, Australia and Europe now offer ECS directly to consumers, often without appropriate genetic pre- and post-counselling[5]. Recently, non-profit health organizations in Australia[6], Belgium[7] and the Netherlands[8, 9] started to initiate ECS for individuals without an a priori increased risk.

In the Netherlands, there are no private providers offering carrier testing and within general health care a standard offer of ECS to prospective parents is lacking[6]. Two academic medical centres developed a non-commercial carrier screening test for 50-70 severe AR disorders. These tests are available for all prospective parents in the Netherlands, paid on their own costs, but are in general not actively offered to them by health care professionals. The Amsterdam University Medical Centres (Amsterdam UMC) panel mainly comprises childhood-onset, severe inborn errors of metabolism (IEMs) for which no or only limited effective disease-modifying treatment is currently available, such as Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome), Tay-Sachs disease and Batten disease[10].

In comparison to targeted screening, preconception ECS maximizes opportunities for autonomous reproductive choices by providing more genetic information and thus more equity of access to carrier testing[11]. However, the implementation of ECS raises several practical, social and ethical concerns, such as downstream medical service costs, psychosocial harms and concerns about potential societal pressure to use ECS[11-14]. Moreover, according to stakeholders, a lack of demand for genetic carrier screening in the general public is an important barrier for implementation[12].

Several studies assessed the attitudes towards ECS among individuals and couples from the general population, suggesting that there is interest among

the target population[8, 9, 15-18]. Recently the study of Nijmeijer et al.[19] showed that relatives of patients with MPS III had more positive attitudes towards ECS than members of the general population, which is in line with the results of other studies assessing attitudes of patients and relatives towards carrier screening for e.g. fragile X syndrome[20, 21], spinal muscular atrophy (SMA)[22], cystic fibrosis (CF)[23, 24] and hemophilia[25]. Involving patients and families in discussions about the implementation of ECS can provide important information, as they may perceive different issues on ECS than the general population[25]. These may include concerns about a decline in future funding of research for potential treatment options and the possible negative shift of public attitudes towards people with a disability[14, 26].

Another aspect associated with the implementation of ECS is the large heterogeneity of ECS panels. The number of disorders included in current panels varies from 40 to almost 1500 disorders[27, 28]. Although European[2], American[1], and Australian[29] guidelines and pilot studies have proposed consensus-based criteria for the composition of panels, major differences were shown in an overview of 16 available (commercial) ECS tests with overlap in only three disorders for all providers[27]. While earlier studies gauged the opinions of (mainly) clinical geneticists or other health care workers on inclusion criteria for ECS panels[29-31], little is known about the opinion of potential users of ECS or by (relatives of) patients affected with genetic disorders towards their desired composition of these panels.

Finally, there is no uniformity in the way how to disclose ECS test results to prospective parents. Results can be disclosed to partners individually (full disclosure of individual test results) or as a couple-based result (individual carrier states are only reported if a carrier couple is identified, i.e. both partners carry a pathogenic variant in the same gene)[2, 32]. Surveys among the general population suggest that most individuals prefer full disclosure of individual test results[9], although most couples do not seem to object towards receiving couple-based results only[32]. However, the considerations on which such preferences are based are unknown.

This qualitative focus group study aims to obtain insight into the perspectives of relatives of MPS III patients and potential users from the general population on ECS, including attitudes towards the offer of ECS, the composition of ECS panels and the disclosure of test results (individual or couple-based), to enrich the discussion on the implementation of ECS. Relatives of MPS III patients were selected as this disorder meets all the international consensus-based criteria for the composition of ECS panels and is included in most ECS panels[1, 2, 29].

Methods

Study design

This study used a focus group design as this enables a setting in which people's feelings, perceptions, and reactions can be carefully assessed[33]. Seven semi-structured focus groups were conducted between May 2019 and September 2019. The study was approved by the Medical Ethics Committee of the Amsterdam UMC, the Netherlands.

Participants

Parents of all MPS III patients currently under treatment in the Dutch national expertise centre received an invitation by email from a member of the research team (response rate 32%) and were subsequently asked to forward this email (introducing the topic) to other relatives, as we did not have their contact details. Therefore, we do not know this response rate. Relatives were compensated for their participation with a gift card of 25 euro and reimbursement of travel costs. First- and second-degree relatives participated in separate focus groups, resulting in three focus groups with first-degree relatives (Group (Gr)#1, N=9/Gr#2, N=4/Gr#3, N=5) and one focus group with second-degree relatives (Gr#4, N=5).

Three focus groups (Gr#5, N=6/Gr#6, N=7/Gr#7, N=5) comprised individuals from the general population who were planning to have (more) children. Participants were recruited by CGselecties, a Dutch research marketing agency that provides a panel of more than 25,000 individuals who are willing to participate in (qualitative) research on a regular basis in return for an incentive of 45 euro. The sample was selected from their panel based on the demographics gender, regional area, educational level, and reproductive age to represent the Dutch population (response rate ~9%). Participants were not informed by the agency about the topic which would be discussed during the focus group.

Focus group guide and procedure

All focus group meetings took place in a meeting room at the Amsterdam UMC and had a duration of approximately 2 h. Six out of seven focus groups were moderated by the same researcher (TC) and one focus group was moderated by another member of the research team (LHe). In each focus group, the moderator was assisted by another member of the research team (LHa, FAW, HvO, IvD).

Before the start of the focus group, the participants from the general population were shown an educational video (https://youtu.be/V9FKDNF_-tI) in which information on AR inheritance, the ECS test for 50 genetic disorders in

the Amsterdam UMC as an example of an ECS test, reproductive options in case of an increased risk (1:4) of affected offspring, and a description of the nature and course of MPS III as an example of a disorder included in ECS panels were provided. The educational video was not shown to relatives as we know that visuals of other MPS III patients may elicit strong and undesired emotional responses in the setting of a focus group meeting, but they received a short presentation with similar information on AR inheritance, the ECS test for 50 genetic disorders, and reproductive options.

The focus group guide was developed by members of the multidisciplinary research team, including experts in psychology, clinical genetics, health sciences and metabolic diseases. The guide consisted of four main topics: reasons (self or others) to accept or decline ECS using the Amsterdam UMC test as an example, awareness on the possibility of ECS, the composition of ECS panels, and preferences in disclosure of test results. Reasons (not) to opt for ECS were discussed and prioritized using post-its. Subsequently, the moderator presented a list of categories to enhance the discussion on the composition of ECS panels, consisting of severe life-threatening disorders that lack treatment, intellectual disability, physical disability, late-onset disorders, and the category ''(prospective) parents are free to choose''. Although a focus group guide was composed, participants were also invited to discuss other topics related to ECS which they considered relevant.

At the end of each focus group session, participants completed a brief questionnaire assessing sociodemographic characteristics (age, gender, educational level, considering a (future) pregnancy, marital status and religious beliefs). Two additional questions assessed familiarity with the Amsterdam UMC carrier test and previous experience with genetic carrier testing in general.

Data analysis

Data collection stopped until data saturation was reached. All sessions were audio recorded and transcribed verbatim without any individually identifiable details to guarantee full anonymity of the participants. The transcripts were analysed with a thematic coding method[34]. Two researchers (TC and IvD) independently analysed the first five transcripts using qualitative software MAXQDA 2020 (VERBI Software, 2019). Relevant parts of the transcripts were marked and codes were generated to organize data into meaningful groups (data was assigned to only one code). Subsequently, themes were identified and codes were assigned to the identified themes. Differences in codes and themes were discussed until consensus was reached. TC subsequently analyzed the remaining two focus groups. The final thematic framework matrices were discussed with

another member of the research group (LHe) until consensus was reached. Finally, the thematic frameworks of the focus groups with relatives of MPS III patients and individuals from the general population were contrasted and compared. Central themes were discussed and illustrated with quotations. For each theme, the most eloquent quotations which were considered exemplar for the themes were chosen and discussed within the research team. Descriptive statistics were performed to describe the sociodemographic characteristics of participants. Characteristics were compared between relatives and individuals from the general population using independent sample T-tests for continuous data and Chi-square tests for categorical data. The Statistical Package for Social Sciences (SPSS) version 25.0 was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA).

Results

Participants

Sociodemographic characteristics of participants and their familiarity with carrier testing are shown in Table 1. In total, 23 relatives of MPS III patients participated including eighteen parents (78.3%), two siblings (8.7%), two aunts (8.7%), and one grandfather (1%). Individuals from the general population (N=18) were significantly younger and more often considered a (future) pregnancy. Relatives of MPS III patients were more often aware of the Amsterdam ECS test for 50 severe genetic disorders compared to participants from the general population, due to the fact that most relatives had also participated in a previous questionnaire study on ECS[19].

Table 1 Characteristics of participants in the focus groups

	All participants	**Relatives**	**General population**	
	N=41 (%)	**N=23 (%)**	**N=18 (%)**	p*
Age in years; mean (SD)	43.0 (15.63)	53.9 (12.73)	29.7 (4.45)	**<.001**
Age categories				
18-24	2 (4.9)	0 (0.0)	2 (11.1)	
25-34	14 (34.1)	1 (4.3)	13 (72.2)	
35-45	9 (22.0)	6 (26.1)	3 (16.7)	
46-76	15 (36.6)	15 (65.2)	0 (0.0)	
Female gender	22 (53.7)	12 (52.2)	10 (55.6)	.83

Table 1 Characteristics of participants in the focus groups *Continued*

	All participants	Relatives	General population	
	N=41 (%)	N=23 (%)	N=18 (%)	p*
Country of birth (Netherlands)	40 (97.6)	22 (95.7)	18 (100.0)	.37
Educational level[a]				.71
Low	4 (9.8)	3 (13.0)	1 (5.6)	
Intermediate	16 (39.0)	9 (39.1)	7 (38.9)	
High	21 (51.2)	11 (47.8)	10 (55.6)	
Religious beliefs[b]				.13
No	20 (48.8)	10 (43.5)	10 (55.6)	
Yes	19 (46.3)	13 (56.5)	6 (33.3)	
I do not want to say	2 (4.9)	0 (0.0)	2 (11.1)	
Marital status				**.01**
Single	7 (17.1)	1 (4.3)	6 (33.3)	
In a relationship / married	34 (82.9)	22 (95.7)	12 (66.7)	
Have child(ren)				**.001**
No	12 (29.3)	2 (8.7)	10 (55.6)	
Yes	29 (70.3)	21 (91.3)	8 (44.4)	
Considering a (future) pregnancy[c]				**<.001**
No	19 (46.3)	19 (82.6)	0 (0.0)	
Yes	22 (53.7)	4 (17.4)	18 (100)	
Have you ever heard of the carrier test for 50 genetic disorders before this focus group?				**<.001**
No	19 (46.3)	3 (13.0)	16 (88.9)	
Yes	22 (53.7)	20 (87.0)	2 (11.1)	
Have you ever taken a carrier test?				**<.001**
No	32 (78.0)	14 (60.9)	18 (100)	
Yes	9 (22.0)	9 (39.1)	0 (0.0)	

* Sociodemographic characteristics were compared between relatives of MPS III patients and individuals from the general population. Significant differences ($p < .05$) are presented in bold

[a] Educational level. Low: primary education, lower vocational education, lower and middle general secondary education. Intermediate: middle vocational education, higher secondary education, pre-university education. High: higher vocational education, university

[b] 'Yes' if answers comprised of the following: 'active religious', 'a little active religious', 'religious, but not active'

[c] 'Yes' if answers comprised of the following: 'I have no children at the moment but I would like to have children', 'I have children and my partner and I would like to have more children', I am / my partner is currently pregnant', or 'I would have liked to have children but I remained childless'

Focus group results

Five evident themes were generated from the data: (1) benefits of ECS, (2) barriers to opt for ECS, (3) disclosure of test results: offering a choice, (4) severity as key criterion for ECS panels, and (5) support for ECS. Results for each theme are described below.

Benefits of ECS

During the focus group discussions, participants reported various benefits of ECS. All arguments in favor of ECS were grouped in four overall categories relating to the interest for prospective parents, for the future child, for the family and for society (illustrative quotes in Table 2). The potential benefit of ECS mentioned by the majority of both relatives and individuals from the general population was that the wide range of reproductive options after ECS could increase prospective parents' autonomy and could provide more assurance of having a healthy child.

> *The [ECS] test allows you to make a choice in advance […], you can choose alternative ways to get pregnant* (general population, Gr#6)

Related to the interest of the future child, both groups stated that ECS may prevent suffering for the child.

> *If it was up to us, she [child with MPS III] was never born. She has to go through so much suffering* (parent, Gr#3)

Only relatives of MPS III patients mentioned that an earlier postnatal diagnosis can be a benefit of ECS, and that ECS offers potential benefits for other family members as well, allowing to prevent suffering for, e.g., siblings of an affected child and offering the option for cascade testing. Although arguments related to potential interest for society were less frequently mentioned, and sometimes accompanied by emotions, saving costs for society by preventing the birth of a child with profound disabilities as well as the feasibility to decrease the prevalence of these disorders were mentioned in both groups.

> *It sounds very harsh, but those costs [for an affected child] indirectly pass on to the rest of the Netherlands, in what they have to pay for healthcare* (general population, Gr#5)

Barriers to opt for ECS

Barriers for the intended uptake of ECS mentioned by participants were allocated into six overall categories relating to a lack of awareness, lack of genetic knowledge, a lack of personal relevance, psychosocial impact, practical barriers and ideology and beliefs (illustrative quotes in Table 3). Individuals from the general population indicated that they had never heard of the availability of ECS and consequently did not consider to participate yet. Moreover, there was little knowledge on the concept of inheritance and confusion about the difference with the non-invasive prenatal test (NIPT) was expressed.

> *Well yes I could do the NIPT-test. But eeeh, the carrier screening test, haven't heard about this. Isn't this test similar to NIPT?* (general population, Gr#7)

Relatives mentioned that the absence of a genetic disorder in the family would probably be the most important barrier for prospective parents without experiential knowledge. Indeed, most participants from the general population evaluated ECS as less relevant for this reason. Some participants perceived the reported risk of having affected offspring (1:600) as low, which led to discussions with others who disagreed.

> *I am healthy, my partner is healthy. Nobody in the family has a disorder. So, I assume in my next pregnancy that the child will be healthy as well […] all reasons why I should not opt for the test, I guess* (general population, Gr#7)

Anxiety and worries about the test results were also mentioned. Some participants preferred a care free pregnancy or were afraid that they would no longer dare to conceive, which would be a reason for them to refrain from ECS.

> *I believe that if you know [that you are a carrier] in advance, that it can drive you crazy if you think about it too much* (general population, Gr#5)

The costs of the test (e.g., 650 euro for the Amsterdam UMC test) were mentioned as a practical barrier and were extensively debated. Both groups expressed the concern that these costs may lead to inequality in access since many people can probably not afford this and they held the opinion that health insurances should (partly) reimburse these costs. Relatives, however, reasoned from an experiential perspective that the costs for ECS compare highly favourable to

the extra costs involved in caring for a child with a severe genetic disorder. Regarding the category ''ideology and beliefs'', a concern expressed by a relative was that genetic technologies might be used to create a world with only perfect people (eugenics).

> *Then it is a problem that people who can afford it will opt for the test, and people who do not have that amount of money will not* (relative, Gr#4)

Disclosure of test results: offering a choice

Participants discussed the pros and cons of both full disclosure of individual test results or only disclosing couple-based test results. Most arguments were similar for relatives and the general population (illustrative quotes in Table 4). Most participants preferred full disclosure of individual test results. In particular, having access to information that can be of importance to the future child or other family members (cascade testing) was considered an important advantage.

> *I would like to tell that information to my children, because, I think it is important that they get tested too* (parent, Gr#3)

Furthermore, participants emphasized the importance of individual test results when changing partners as it was considered undesirable to have and pay for another test in case of a new partner. Moreover, ''the right to know'' as much as possible about your own biological material or when having paid for the test out-of-pocket, was suggested as reasons in favor of reporting individual test results.

Some participants expressed a preference not to be burdened by individual test results because it might cause unnecessary anxiety about one's own health. Another reason to prefer couple-based test results was feeling a commitment towards the partner, because ''as a couple'' you embark on the adventure of having children.

Participants in several groups suggested to give people the choice between individual results or couple-based test results to increase their autonomy. Additionally, it was suggested to offer full disclosure of test results at higher costs.

> *Maybe it is a solution to give people the choice themselves which option they prefer. Because if one partner does not want to know all the information, but the other does, then you can choose*
> (general population, Gr #1)

Severity as key criterion for ECS panels

All participants agreed that childhood-onset and life limiting disorders for which no disease-modifying treatment is available should be included in ECS panels. Disease severity was often mentioned as criterion to decide which types of disorders (e.g., only physical disabilities or intellectual disabilities or both) should be included in screening panels. Relatives mentioned that it can be challenging to determine if disorders are ''severe enough'' to include in screening panels as some genetic disorders, including MPS III, are associated with a variability of disease expression and you cannot always reliably predict the course of the disease before birth.

> *The first time we met a couple who's child also had MPS III, the mother came up to us immediately and told us that her child still took swimming lessons and everything, while our son couldn't do this at all. Our son is now 25, while her child has become no older than 16. And then I think, how is that possible? […] It cannot be predicted* (parent, Gr#1)

The perceived severity of a disease, according to participants, was related to (1) self-sustainability; (2) if the child would be in pain; (3) if the child would have to undergo medical procedures; and (4) if ''the child could really be a child''. It was noticeable that individuals from the general population more often classified disorders as severe and suitable to include in ECS panels compared to relatives. For example, relatives classified other disorders, such as congenital blindness and deafness, as relatively mild compared to the severity of MPS III and considered such disorders not severe enough to be included in the panel, while participants from the general population believed they could be included.

All participants expressed serious doubts concerning the inclusion of late-onset disorders in screening panels. Some participants said that late-onset disorders are part of life and that one should not try to play for God. Others stated that they did not want to deprive their child of a carefree childhood. On the one hand, some participants supported the possibility that one should be free to select which disorders or categories of disorders one would like to have included in an ECS panel.

> In my opinion, you can offer it [optional disorders and categories of disorders] and then everyone can decide for themselves (general population, Gr #1)

On the other hand, other participants were concerned that free choice of disease (categories) might lead to unwanted ''designer babies''.

> *No, then you go shopping [for which disorder you prefer screening]. I find this very difficult to consider. It shouldn't be a lottery. Then you go back to that designer [baby] argument. Well, I think that, I think that's too much*
> (parent, Gr#1)

Support for ECS

All participants had a positive attitude about ECS and considered the offer of such a test important for all prospective parents. Moreover, they believed that ECS should be made available more actively, for example by health professionals such as the general practitioner and via specialists. To increase awareness about ECS, participants believed the government should have a leading role and suggested to make use of commercials, banners, social media, information on contraceptives and flyers. Moreover, high school was mentioned as setting in which teenagers could be informed for the first time about the availability of ECS.

> *Maybe first a big national campaign and after this, smaller initiatives should be initiated to keep the information up-to-date. I think the majority of people does not know anything [about ECS]"*
> (general population, Gr#5)

Table 2 Benefits of ECS mentioned by relatives and the general population with representative quotes

Themes	Exemplar quotes
Interest for prospective parents	
Offers (reproductive) choices for future parents	*If I have to tell my children why they should get tested, I would say: because you are able to choose if you want to intervene if there is something wrong with the fetus* (parent, Gr#2)
Prevents suffering for the parents[a]	*Nobody wants to survive their own child. We [parents of a child with MPS III] all woke up a thousand times at night hoping that it was just a dream [their child being severely ill], but unfortunately the nightmare was not over* (parent, Gr#2)
Mentally or practically prepare for a child with a genetic disorder	*But otherwise you are prepared for your child to be ill, maybe that will make a difference mentally (parent,* Gr#3) *You may have to work fewer hours because you should be able to take care of your child* (general population, Gr#5)
Fear or regret[b]	*If there is something wrong [with your child], and you realize you had the opportunity to reduce the risk* (general population, Gr#6)
Information about your own health status[b]	*Getting insight into the status of your own health [...], the test provides some sort of insight* (general population, Gr#7)
Being prepared as partners[b]	*Being on the same page in advance [...]That may prevent future arguing, because you both knew it beforehand* (general population, Gr#5)
Interest for the future child	
Prevents suffering for the child (by preventing the birth of an affected child)	*I think preventing suffering for such a child is the most important reason of all* (general population, Gr#5)
Information that allows earlier diagnosis and/or treatment after birth[a]	*If we had known the diagnosis from birth, we had acted very differently [towards the child]. So, then the test is also useful, if you choose not to intervene* (parent, Gr#1)

Table 2 Benefits of ECS mentioned by relatives and the general population with representative quotes *Continued*

Themes	Exemplar quotes
Interest for the family	
Prevents suffering for the family (by preventing the birth of an affected child)[a]	*I do not think it only prevents suffering for the child, but also for the whole family* (parent, Gr#2)
Cascade testing	*The test results offer you the opportunity to warn other family members; they may also be at increased risk* (parent, Gr#3)
Interest for the society	
Saves costs for society	*You can have a discussion about how socially responsible it is to bring a disabled child into the world when you consider the costs* (relative, Gr#4)
To decrease the prevalence of genetic disorders	*To prevent that every year in the Netherlands there are still some children born with the disorder* (parent, Gr#2) *That such diseases can be eradicated (general population,* Gr#5)
Decreases the burden on the health care system[a]	*If you prevent the birth of children with severe disorders, you will also relieve the burden of the healthcare system dramatically. Because, uh, we spend a lot of time in the hospital* (parent, Gr#1)

Arguments are both mentioned by relatives of MPS III patients and individuals from the general population

[a] Argument only mentioned by relatives of MPS III patients

[b] Argument only mentioned by individuals from the general population. Gr, group

Table 3 Barriers of ECS mentioned by relatives and the general population with representative quotes

Themes	Exemplar quotes
Lack of awareness	
Lack of awareness about the availability of ECS	*Do people even know it [ECS test] exist? If it is not offered, or you have not heard about it, you automatically will not participate (parent, Gr#1)* *I think most people have not heard about the test. Why? What is the reason that it is not known yet?* (general population, Gr#6)
Ignorance about health risks for offspring	*I think you do not even realize that eh, when I was pregnant of my first child [healthy sibling] I never thought there could be anything wrong (parent, Gr#3)* *When I was pregnant of my first child, I was not concerned at all. Only fun and excitement [..] That is the unawareness that a lot of people have; babies are born healthy right?* (general population, Gr#6)
Lack of genetic knowledge	*''What is the reason they do not include Down Syndrome in the [ECS] test? Why is that not possible?''* (general population, Gr#6)
Lack of personal relevance	
Absence of a genetic disorder in the family	*Honestly if it [genetic condition] does not occur in your family or circle of friends, you will not think about it''* (relative, Gr#4) *There is no history of diseases known in my family* (general population, Gr#7)
Low perceived risk	*For me the risk feels negligible [for the other 49 disorders], it is 1:600 and I think that is approximately 0.17 percent? Well, 0.17 percent is negligible* (relative, Gr#4) *If you see so many healthy people and so few disabled people, it feels like you have a very small chance. [...] It just feels like 1:6000 instead of 1:600. I also think 1:600 is a pretty small chance, but if I compare it with something else like, uh, like the chance that an airplane will crash, then I would think, I would not fly* (general population, Gr#5)

Table 3 Barriers of ECS mentioned by relatives and the general population with representative quotes *Continued*

Themes	Exemplar quotes
Psychosocial impact	
Test offer/results leads to anxiety and worries	*That you are suddenly completely mentally confused, [...], that you may be a carrier of 10 disorders* (parent, Gr#2)
Being confronted with difficult decisions	*The dilemma of what to choose in case of a positive test result (relative, Gr#4)* *It is of course stressful, choices have to be made* (general population, Gr#6)
Disagreement or friction with partner	*Partner does not want to opt for ECS* (parent, Gr#3) *One partner wants to take the risk, the other partner does not [...]. Then there will be conflicts* (general population, Gr#5)
Practical barriers	
Costs of the test	*As much as I would like to know, I cannot afford it. [...] We would have to save money to cover those extra costs* (general population, Gr#6)
The test does not provide a 100% guarantee of having a healthy child	*This test includes 50 disorders, there are many other disorders for which you may be at an even greater risk* (relative, Gr#4) *Even though they told you that nothing is wrong, it is not 100% certain (general population*, Gr#5)
Ideology and beliefs	
Religious beliefs (reproductive options are not an option)	*I would not opt for the test, but eh, that is only because of our religion (parent, Gr#3)* *If God wants your child to be ill you should leave it that way, some people might think* (general population, Gr#5)
Every child is welcome[b]	*Children with an illness also have the right to be born* (general population, Gr#5)
Fear of eugenics ''perfect baby''[a]	*The risk of preparing a perfect human being* (parent, Gr#1)
Unnatural[a]	It is unnatural. Not everything can be planned (relative, Gr#4)

Arguments are both mentioned by relatives of MPS III patients and individuals from the general population

[a]Argument only mentioned by relatives of MPS III patients

[b]Argument only mentioned by individuals from the general population. Gr, group

Table 4 Mentioned arguments regarding full-disclosure of test results versus couple-based test results

Themes	Exemplar quotes
Full disclosure of test results	
Important information for children and other family members (cascade testing)	*I would like to know if I am a carrier, because my child could also be a carrier (general population,* Gr#5)
Avoid testing again in case of a divorce / split up with partner	*I would prefer receiving my own result, because things can go wrong [in case of relationships] and then you would have to test yourself again if you have another partner* (relative, Gr#4)
It is my right to get all results	*I mean, you both give your blood as individual [for the test], so I think that you also should get your results individually. [...], but if you pay E650,- out of pocket you want to know everything* (general population, Gr#7)
Curiosity	*I am just curious about the result. You do not choose to do this test for no reason. When I would do this test, I would like to know if I am a carrier* (parent, Gr#2)
Relevant for sperm donor or woman who want to freeze their eggs	*Women [with a desire to conceive] who do not have a relationship yet, and for example want to freeze their eggs or need a sperm donor, would also want to know if they are a carrier. And maybe it is also relevant to test the donor then* (general population, Gr#6)
Couple-based test results	
Individual information leads to anxiety	*If you are very anxious, if you are sensitive for that [being anxious], you might worry about suffering [from one of the diseases]* (general population, Gr#5)
Consequences of being both carrier of the same disease is only relevant	*I would opt for this [couple-based] because what is the purpose of knowing all those diseases? You are only interested in the match* (parent, Gr#3)
Commitment to partner	*I would choose as a couple, because, well, there is your risk, in that match. Call me a romantic, but you sit there as a couple, as a couple you want a child [...] And it is better not to know what you do not need to know* (relative, Gr#4)

Discussion

This study explored the perspectives of relatives of MPS III patients and members of the Dutch general population on several important aspects related to preconception ECS. As the current study used a qualitative focus group design, we were able to further assess the motives, considerations, and feelings of relatives of MPS III patients and the general population about ECS, related to the opinions as reported in earlier survey studies on ECS[9, 19].

Despite initial confusion about its purpose, both relatives of MPS III patients and individuals from the general population supported an offer of ECS to all prospective parents in the Netherlands. Participants mentioned the benefits of ECS for prospective parents, but also emphasized the benefits from other perspectives (i.e., the future child, family, and society). These positive views are in agreement with the results of earlier survey studies on the attitudes of relatives of MPS III patients[19] and the general population[8, 9, 16, 18]. Participants in our study believed that the population needs to be more actively informed about the availability of ECS, which underpins their positive attitudes.

Discussing the benefits of ECS, only relatives of MPS III patients mentioned an earlier postnatal diagnosis as a possible benefit of ECS. This outcome is likely related to a long diagnostic delay experienced by many parents of MPS III children[35]. Furthermore, only relatives mentioned benefits of ECS for other family members, as they know from experiential perspective that a severe genetic disorder may have significant psychosocial impact on the whole family[36].

Despite positive attitudes, participants mentioned significant barriers for implementation. The out-of-pocket costs associated with ECS testing were seen as an important barrier to participate in ECS and could result in inequality in access. Currently, ECS for prospective parents in the Netherlands without a medical indication, for example a positive family history, belonging to an ancestry-based or geographically based high risk group, is not reimbursed by health insurance companies. Previous studies in the Netherlands[8, 9], Australia[16] and the UK[37] showed that most prospective parents are willing to pay a maximum of approximately 50-150 euro, whereas the current costs of ECS in many countries worldwide are much higher. In accordance with previous studies[9, 19, 38, 39], a lack of perceived personal relevance due to the absence of a genetic disorder in the family was believed to be an important reason for people to refrain from having ECS. Initiatives to inform couples planning a (near) future pregnancy about the rationale of ECS (e.g., aiming at couples without positive family history), for example with public education- or awareness campaigns, are essential and were encouraged by all participants in our study. In line with

our findings, Holtkamp et al.[12] showed that Dutch key stakeholders including those working in the field of carrier screening believed that more awareness of ECS and genetic disorders included in screening panels could overcome a lack of demand among the general public as well.

Concerns about social stigmatization or discrimination are frequently mentioned in discussions about the acceptability of carrier screening[11]. Although offering ECS to the general population might reduce stigmatization of specific ethnic groups compared to ancestry-based panels, expanded screening panels could reinforce the stigmatization of disabilities in general[11, 26]. In the current study, however, relatives of MPS III patients did not mention concerns about any form of stigmatization. The strong positive attitudes of MPS III relatives towards ECS may be related to the neurodegenerative and progressive course of MPS III, which places a significant burden on the child and the family[40, 41]. Boardman et al.[22] showed in their study on the views of affected families towards population screening for SMA that attitudes towards screening were highly correlated with quality of life (QoL) rated by patients themselves or by their family members. Those perceiving the lowest QoL were most likely to support the implementation of ECS for SMA compared to those perceiving a good QoL.

In all focus groups, the majority of participants preferred full disclosure of individual test results instead of couple-based results. This is in accordance with previous studies on the attitudes towards ECS[9] and carrier screening for CF[42]. An innovative suggestion of participants in the current study was to give (prospective) parents the choice. However, such a choice option may be challenging in practice. Moreover, full disclosure of test results may be less feasible when screening for a high number of variants due to the complexity and costs of providing (post-test) counselling for a relatively high amount of disorders, as it is estimated that every individual is carrier of ~20 AR disorders[43]. Couple-based test results are expected to reduce the impact on workload and costs in the laboratories, and the amount of work and costs associated with subsequent genetic counselling[44, 45]. However, the limited possibility for cascade testing in families in case of couple-based test results can also be perceived as a disadvantage, in particular for more common disorders such as CF[46]. This drawback may be overcome by additionally communicating only those disorders with higher carrier frequencies on an individual basis, as recently implemented in Belgium[47]. All participants agreed that severe childhood-onset disorders which substantially impair QoL, such as MPS III, should be included in ECS panels. In accordance with recommendations of the European Society of Human Genetics[2] and a recent study on the development of the gene panel for the Australian

Reproductive Genetic Carrier Screening Project[29], disease severity was the most important characteristic when considering disorders suitable for screening.

Individuals from the general population more often classified disorders as severe and suitable to include in ECS panels compared to parents of MPS III patients. A discrepancy in perceptions of disease severity was also found in the study of Boardman et al.[48], in which the general public had a more negative view of SMA compared to families themselves. The influence of experiential knowledge on perceptions of disease severity should be considered when drafting future policy decisions regarding the composition of ECS panels.

Opinions in the focus groups were divided on whether to give prospective parents the opportunity to choose from a list of individual disorders or to choose from different panels, for example categories of disorders similar in type or severity as suggested by Kraft et al[49]. Genetic professionals in the study of Chokoshvilli et al.[30] believed that offering individual couples a choice of disorders for which they would like to be screened is not feasible in a population screening setting as it may be complicated for prospective parents without prior experience to understand individual disorders. This is in accordance with a previous study assessing health professionals' preferences towards the NIPT offer[50]. Moreover, many genetic disorders included in ECS panels have a wide variation in severity which cannot predetermined with ECS. Counselling potential users on all individual disorders and their phenotypic variation would not be feasible within the time currently available. As this might jeopardize informed decision-making, a model of generic consent has been proposed to meet this challenge[51].

Some limitations of the current study need to be discussed. First, the perspectives of relatives of MPS III patients may not be generalizable to relatives of patients with other genetic disorders included in ECS panels, as previous studies suggest that disease severity affects the attitudes of patients and their family members towards preconception ECS[22, 25]. Second, more than half of the participants were highly educated which is not a reflection of the general population in the Netherlands. However, the association between educational level and interest in ECS is unclear[8, 9, 15, 16, 39]. Third, response bias may have occurred if relatives who support ECS implementation and who previously participated in the survey study were more likely to attend the focus groups. Although many relatives of MPS III patients already participated in the previous survey study on ECS, we did not observe any differences in their understanding or attitudes compared to relatives who did not. Fourth, the way in which we explained the concept of ECS to members of the general population and relatives of MPS III patients was not equal as relatives of MPS III patients were not shown the educational video[52]. Since relatives were shown a short presentation on the

concepts of inheritance included in the educational video and presumably had more genetic knowledge at baseline than the general population[19], bias likely has been kept to a minimum. Finally, participants with stronger voices might have dominated the discussion resulting in 'false consensus', which we aimed to avoid by carefully moderating the discussions.

Conclusion

In conclusion, this focus group study provided valuable insights that can enrich the discussions on the implementation of preconception ECS. It is shown that both relatives of MPS III patients and individuals from the Dutch general population support further implementation of preconception ECS to prospective parents without an a priori increased risk, especially for severe, childhood onset disorders. However, important barriers for ECS implementation were identified. The concept of ECS was difficult to grasp for participants, especially for individuals from the general population. Educating prospective parents about the concept of ECS and the type of disorders included in ECS panels is essential for creating awareness and ensuring an informed choice when offering ECS.

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‘Welkom in de wereld die er nog niet is, de wereld van de toekomst’

- Putrajaya (bordje in stad in Maleisië)

CHAPTER 4

Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer

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Abstract

Preconception carrier screening offers couples the possibility to receive information about the risk of having a child with a recessive disorder. Since 2016, an expanded carrier screening (ECS) test for 50 severe autosomal recessive disorders has been available at Amsterdam Medical Center, a Dutch university hospital. This mixed-methods study evaluated the experiences of couples that participated in the carrier screening offer, including high-risk participants, as well as participants with a general population risk. All participants received genetic counselling, and pre- (n=132) and post-test (n=86) questionnaires and semi-structured interviews (n=16) were administered. The most important reason to have ECS was to spare a future child a life with a severe disorder (47%). The majority of survey respondents made an informed decision (86%), as assessed by the Multidimensional Measure of Informed Choice. Among the 86 respondents, 27 individual carriers and no new carrier couples were identified. Turn-around time of the test results was considered too long and costs were perceived as too high. Overall, mean levels of anxiety were not clinically elevated. High-risk respondents (n=89) and pregnant respondents (n=13) experienced higher levels of anxiety before testing, which decreased after receiving the test result. Although not clinically significant, distress was on average higher for carriers compared to non-carriers ($p<0.0001$). All respondents would opt for the test again, and 80.2% would recommend it to others. The results suggest that ECS should ideally be offered before pregnancy, to minimize anxiety. This study could inform current and future implementation initiatives of preconception expanded carrier screening.

Introduction

Carrier screening is used to investigate whether a couple has an increased risk of having children with a severe autosomal and X-linked recessive genetic disorder in order to facilitate reproductive decision making. Ideally, carrier screening is offered before pregnancy to allow for a maximum number of reproductive options, including preimplantation genetic testing (PGT) and prenatal diagnosis (PND).

Historically, screening initiatives were mainly ancestry based, addressing individuals from specific ethnic groups with a known increased risk for particular recessive inherited conditions. Due to the development of next generation sequencing, screening for large panels of recessive conditions became possible at lower costs, resulting in carrier screening being increasingly offered to the general population, i.e., universal expanded carrier screening (ECS) [1,2]. Several benefits of universal ECS compared to ancestry-based screening for high-risk populations have been proposed, such as equity of access to screening and the potential reduction of stigmatisation of ethnic groups [3]. However, disadvantages of ECS are the potential higher costs due to increased testing of broader panels, workload, and the possible emotional impact of test results [2]. Moreover, disability rights groups have expressed criticism towards the availability of ECS because of its tendency to negatively shape public opinion about disabilities [4,5].

Worldwide, ECS panels are mainly offered by commercial companies, which have been criticized for using persuasive language, not providing complete information, and offering only optional genetic counselling [6]. Increasingly, non-profit healthcare initiatives are emerging, yet large differences between initiatives and countries exist [7,8] leading to questions about how ECS should be offered and by whom. Several expert bodies have been drafting recommendations on how ECS can be responsibly implemented, emphasising the importance of accurate and complete information provision, appropriate education of health professionals, and the need for research into public perceptions on ECS and its psychological impact [1,2,9].

To our knowledge, the majority of literature assesses the hypothetical interest in ECS [10] and few studies have been conducted among users of ECS [11-14]. Research on the impact of carrier screening for a single autosomal recessive disease, cystic fibrosis (CF), has shown that identified carriers generally have no adverse long-term psychological consequences [15]. However, some studies showed that health perception was negatively influenced after screening, along with increased anxiety and inability to recall test results accurately [13,16]. Moreover, it has been questioned whether people can make a sufficiently in-

formed decision if there are multiple conditions in one panel, that can cause an information overload [2]. One study that investigated the impact of ECS showed that respondents with negative test results generally did not experience long-term negative emotional impact, and only reported heightened anxiety while waiting for the test results [13]. Additional studies have shown that the information from ECS could relieve uncertainty and anxiety [17], was of value to participants [11,18], and led to informed reproductive decision-making [19]. Reasons to have ECS among both high-risk groups and the general population need further investigation [10]. In the Netherlands, two university hospitals have developed preconception ECS tests for the general population [20,21]. The Amsterdam University Medical Centers, location Academic Medical Center (AMC) Amsterdam has offered a test for 50 severe autosomal recessive disorders since 2016, and the University Medical Center Groningen offers a test for 70 autosomal recessive disorders.

In this study, we investigate experiences of ECS test participants at the AMC hospital Amsterdam, who agreed to participate in a survey or interview study, from both high-risk groups and the general population in terms of reasons to opt for the test, whether choices were informed, psychological well-being before and after the test, changes in reproductive intentions, and satisfaction with the test.

Materials and Methods

Study design

A mixed-methods parallel design was used to evaluate the Amsterdam ECS offer including a survey study using pre-test (Q1) and post-test questionnaires (Q2), and semi-structured interviews to gain an in-depth understanding of participants' experiences [22]. Approval for this study was obtained from the AMC Medical Ethics Review Committee (W16_131#16.152).

Sample population and setting

Couples or individuals interested in the ECS test applied for participation via online registration on the AMC website (www.dragerschapstesten.nl, accessed 13 March 2021) or were referred by a physician (high-risk couples only). The ECS participants, who also participated in the current study, all received pre-test genetic counselling at the AMC, supported by a leaflet and online information. Only one couple decided not to have the ECS test after counselling and did not participate in the survey study. The ECS test is available for all couples planning a pregnancy for a fee (€650 per test) and are reimbursed for high-risk couples

by insurance, except for the 'own risk' excess (€385 per year). Participants were assigned as *high-risk group* if they had an increased risk of being a carrier (couple) for one or more of the 50 disorders based on a positive family history, consanguinity, ancestry and/or geographical background (i.e. people at risk for hemoglobinopathy, individuals living in a specific Dutch genetically isolated community (founder population), and those from Ashkenazi Jewish descent). Participants from the general population were assigned as *general-risk group*. Respondents could opt for parallel (both partners simultaneously) or sequential testing (one partner first, second partner only after the first partner tested positive).

Survey and measurements

Q1 was administered after pre-test genetic counselling to 171 test participants (involving 69 couples and 33 individuals), between May 2016 and May 2018. Q2 was sent to participants' home addresses after they received all the test results. The questionnaires were developed by a multidisciplinary research group consisting of health scientists and clinical geneticists and based on earlier studies [23]. Topics addressed were: (i) reasons to have the test, (ii) informed choice, (iii) recall and understanding of test-results, (iv) psychological well-being (anxiety, worry, distress, health perception), (v) reproductive intentions, and (vi) satisfaction (see Supplement S1 for questionnaire items). *Reasons for having the test* were assessed by the question 'What was the main reason to opt for the preconception carrier screening test for 50 hereditary diseases?'. Respondents were asked to select one answer from a list of nine reasons. *Informed choice* was measured based on the Multidimensional Measure of Informed Choice (MMIC) [24], which defines a choice as 'informed' when respondents had a positive attitude towards ECS, a good level of knowledge and took the test, or had a negative attitude, good knowledge and declined the test. Attitude was measured using a 4-item semantic differential 5-point scale divided into three equal categories (positive, neutral and negative). Respondents with a neutral attitude were removed from the analysis based on literature [24,25]. Knowledge was measured by eight questions. The cut-off for sufficient knowledge was set at 75% (6/8 questions), based on literature [25]. *Recall of test results* was assessed in Q2: 'Do you remember the result of the carrier screening test for you and/or your partner?'. The answers were verified with the actual test result. *Anxiety* was measured with the Dutch 6-item Spielberger State-Trait Anxiety Inventory (STAI) scale [26] during Q1 and Q2. Scores can range from 20-80. A score >40 was considered clinically relevant [27]. *Worry* was assessed in Q2 'I felt worried while waiting for the test result'. The Impact of Event Scale (IES) subscale in-

trusion (the extent to which people relive feelings, dreams or experiences) was used to measure *distress* after screening test-results in Q2 [28]. IES subscale scores range from 0 to 21. A score of >9 was considered a high level of intrusion [29]. *Health perception* was measured in Q2 by asking if respondents felt less healthy after receiving the test result. *Reproductive intentions* were assessed in Q1, asking whether respondents expected that the test result would help with making decisions about having children, and again in Q2, whether their decisions changed after the ECS results. *Satisfaction* was measured with regard to experiences with the ECS itself, whether people would opt for the test again and recommend it to others. Opinions on counselling and costs were assessed in Q1, and opinions on waiting time in Q2.

Interviews

Participants were invited for an interview at random (n=66). Semi-structured interviews were conducted over a period of five months in 2017 by one researcher [H.R.]. All interviewees signed informed consent forms. The interviews explored in-depth experiences with the ECS including reasons to have the test, psychological impact and satisfaction (Supplement S2).

Data analysis

For the questionnaire data, descriptive analysis was done to outline the respondents' characteristics. Respondents were treated as individual subjects since each partner of a couple could have different perceptions [30]. Chi-square tests ($\chi 2$) and t-tests were done to investigate whether there were significant differences before (Q1) and after receiving ECS-results (Q2) between different subgroups. Depending on the outcome variable or when the data was not normally distributed, a Wilcoxon's rank sum test was used. To assess differences between groups and associations of variables with higher STAI scores following Q2, a linear regression analysis using analysis of covariance with a correction for the pre-test STAI scores (Q1) was carried out. The beta coefficients and confidence intervals reflect to what extent STAI scores decreased or increased. P values <0.05 were considered to be significant. All analyses were performed using IBM SPSS version 24.0. Interview transcripts were processed for content analysis by two researchers independently [H.R. and I.v.D.] using thematic analysis with the program MAXQDA.

Results

Characteristics of respondents

Q1 was returned by 140/171 (82%) ECS test participants and Q2 by 94/138 (68%). Eight people were excluded from the analysis due to missing data, resulting in 132 respondents for Q1 (22 individuals and 55 couples), and 86 respondents for Q2 (16 individuals and 35 couples). The characteristics of 89 high-risk and 43 general-risk respondents who completed Q1 are presented in Table 1. A total of 16/66 (24%) invited individuals were interviewed, n=11 females and n=5 males; four interviewees had an a priori high-risk of being a carrier.

Table 1. Survey respondents characteristics

	High-risk group n=89	General-risk group n=43	Total n=132
Sex, n (%)			
-Female	51 (57.3)	22 (51.2)	73 (55.3)
-Male	38 (42.7)	21 (48.8)	59 (44.7)
Age in years, mean (SD)			
-Female	30.1 (4.4)	33.3 (3.9)	31.0 (4.5)
-Male	34.4 (7.8)	35.7 (5.1)	34.8 (6.7)
Ethnicity[a], n (%) missing 2			
-Dutch	58 (65.2)	36 (87.8)	94 (72.3)
-Other Western	6 (6.7)	2 (4.9)	8 (6.2)
-Non-Western	25 (28.1)	3 (7.3)	28 (21.5)
Education[b], n (%), missing 2			
-Low	2 (2.2)	1 (2.4)	3 (2.3)
-Intermediate	20 (22.5)	3 (7.3)	23 (17.7)
-High	67 (75.3)	37 (90.2)	104 (80.0)
Religiously active[c], n (%), missing 3	41 (46.5)	5 (12.1)	46 (35.7)
Have child(ren), n (%), missing 2	26 (29.9)	10 (23.3)	36 (27.7)
Relationship status, n (%), missing 1			
-Married or cohabiting	78 (87.7)	41 (97.6)	119 (90.8)
-Single	8 (9.0)	1 (2.4)	9 (6.9)
-Other relationship[d]	3 (3.4)	-	3 (2.3)
Pregnant (partner or self) at time of testing[e], missing 2	8 (9.2)	5 (11.6)	13 (10.0)

Table 1. Survey respondents characteristics *Continued*

	High-risk group n=89	General-risk group n=43	Total n=132
A priori high-risk[f]			
-Positive family history[g]	89 (67.4)	-	89 (67.4)
-Consanguinity	30 (33.7)		30 (33.7)
-Ancestry:	26 (29.2)		26 (29.2)
Genetically isolated community	8 (9.0)		8 (9.0)
Ashkenazi Jewish	13 (14.6)		13 (14.6)
Hemoglobinopathy	13 (14.6)		13 (14.6)
Applied for ECS consultation, missing 5			
-Actively signed up through website	25 (29.8)	40 (93.0)	65 (51.2)
-Referred by a doctor	59 (70.2)	3 (7.0)	62 (48.8)

[a] Based on Central Bureau of Statistics Netherlands definition.

[b] Low: elementary school, lower level of secondary school, lower vocational training; Medium: higher level of secondary school, intermediate vocational training, High: high vocational training, university.

[c] Religions included: Islam n=16, Roman Catholic n=16, Judaism n=8, Protestant n=4, Buddhist n=1 and other religion n=1.

[d] Engaged n=1, in a relationship not living together n=2.

[e] In the high-risk group 2 couples and 4 individual respondents indicated to be pregnant. In the general-risk group 2 couples and 1 individual respondent indicated to be pregnant.

[f] A priori high risk: of being a carrier or carrier couple. Respondents could have multiple medical indications.

[g] The familial disorders were: Alpers disease n=2, Batten's disease n=2, Cystic Fibrosis n=8, Krabbe disease n=6, Pompe disease n=4, Spinal Muscular Atrophy n=8.

Abbreviations: ECS=expanded carrier screening, SD=standard deviation

Reasons to have the test

The most important reason to have the test for both the high-risk and the general-risk group was to spare the future child a life with a severe disorder, 50.6% and 43.9% respectively (Table 2). Overall, 12.5% reported they were afraid they would regret it if they chose not to have the test. The least important reason to have the test for the high-risk group was to prepare for a child with one of the 50 disorders (2.3%). In the interviews, some participants mentioned that they chose to have testing because they wanted to avoid a difficult life for their child or did not want a (or another) child with a severe disorder: *"I have a child with some issues [...]. We thought let's do it [ECS]. So, I was one of those people who did not do the test out of curiosity, we did the test to exclude that it [having an affected child] would happen again."* (Man, high-risk group, #10). One woman mentioned that being aware of ECS and not opting for it would result in guilty feelings if a child with a disorder was born: *"It may be a bit neurotic, but if I*

know that such a test exists, and I can do it, and I've got the money for it, then… If the baby would have a disorder and I would not have done the test, then I would feel guilty. That's maybe a bit strange, but it played a role." (Woman, general-risk group, #5).

Table 2. Main reasons for respondents to have the preconception expanded carrier screening test

Reasons	High-risk group, n=89 n (%)	General-risk group, n=43 n (%)	Total, n=128 n (%)
I want to spare my child a life with a severe disorder	44 (50.6)	18 (43.9)	62 (53.1)
To avoid having a child with one of the disorders	19 (21.8)	17 (41.5)	36 (28.1)
Fear to regret afterwards when I do not have a test	10 (11.5)	6 (14.6)	16 (12.5)
Perceiving a high risk of being a carrier	15 (17.2)	-	15 (11.7)
Perceiving a high risk of having a child with one of the disorders	12 (13.8)	1 (2.4)	13 (10.2)
On the advice of others, namely...[a]	7 (8.0)	-	7 (5.5)
My partner wants it	4 (4.6)	1 (2.4)	5 (3.9)
For my own children (if they want children)	5 (5.7)	-	5 (3.9)
To prepare for a child with one of the disorders	2 (2.3)	-	2 (1.6)
Other reasons[b]	5 (5.7)	4 (9.8)	9 (7.0)

Percentages do not add up to 100% because respondents could fill in more than one reason. In each group there were n=2 missing.

[a] General practitioner (n=3), parents (n=2), medical specialist at fertility clinic (n=1), clinical geneticist (n=1).

[b] Consanguinity (n= 3), interested in knowing risk (n=3), (deceased) child with one of the 50 diseases (n=2), test is obligatory in other countries (n=1).

Informed choice

Knowledge levels were significantly higher within the general-risk group: 97.7% had sufficient knowledge, compared to 83.1% of the respondents in the high-risk group (p=0.017). Overall, 98% had a positive attitude towards having the ECS. Informed choice analysis showed that 86% of the respondents made an informed decision, which was not significantly different between the high-risk (81.5%) and general-risk group (94.3%) (p=0.81). Uninformed choice was mostly explained by having poor knowledge (Table 3).

Table. 3. Informed and uninformed choice for high-risk and general-risk respondents

	Knowledge	Attitude	Uptake[b]	High-risk group (n= 65)	General-risk group (n= 35)	Total
Informed[a] choice	Good	Positive	Yes	81.5%[c]	94.3%[c]	86%
Uninformed choice	Good	Negative	Yes	1%	-	1%
	Poor	Positive	Yes	17.5%	5.7%	13%
	Poor	Negative	Yes	-	-	-

[a] An informed choice was made when respondents had a positive attitude towards expanded carrier screening, a good level of knowledge (75% correct answers) and took the test.

[b] All respondents agreed to have the test.

[c] Respondents with 'neutral attitudes' (n=25) and missing on this variable (n=6) were excluded from the analysis, based on van den Berg et al. [24].

Recall and understanding of test results

Among the high-risk and general-risk respondents, 61.2% (30/49) and 75.6% (28/37) opted for sequential testing, respectively. The other respondents opted for parallel testing. All participants received full disclosure of their individual ECS test results. No new carrier couples were identified among the survey respondents, seven couples already knew they were a carrier couple because they already had an affected child, and 27 carriers were identified (Table S4 and S5). Of the carriers, 92.6% (25/27) correctly recalled their own test result and that of their partner. One couple falsely indicated that they were a carrier couple of one of the 50 conditions included in the ECS, while they were carriers of another disorder not included in the test. Of the carriers, 37% (10/27) falsely reported that they had no chance of having a child with one of the 50 disorders from the test while there is always a residual risk. For those not identified as carriers ("non-carriers") and not tested respondents, this was 27.1% (16/59). After testing, overall knowledge slightly increased with a mean sum score of 6.97 [SD: 1.26] at Q1 to 7.37 [SD: 1.14] at Q2, although this difference was not significant (p=0.233).

Impact on psychological well-being

Figure 1 shows mean STAI-scores for the different groups. Overall, mean anxiety scores were not clinically elevated. The high-risk group had higher anxiety levels 35.3 [SD 10.8] before receiving the test results compared to the general-risk group 30.5 [SD 10.1] (p=0.03). Pregnant respondents had significantly higher anxiety 40.3 [SD 12.7] before the test result compared to non-pregnant respondents 32.3 [SD 10.4] (p=0.01). Before testing, clinically significant STAI scores (>40) were found for 28/129 (21.7%) respondents [range 43.3-66.5], of which 23 were high-risk couples and four were pregnant. Overall mean STAI scores of respondents significantly decreased after receiving test results from 33.2 [SD 10.9] at Q1, to 26.9 [SD 8.9] at Q2 (p<0.0001). There was no significant difference in anxiety between carriers 27.9 [SD 9.0] and non-carriers 26.49 [SD 8.9] after receiving the test result (p=0.214). At Q2, 6/86 respondents (6.9%) showed clinically elevated STAI scores [range 43.3-66.5], of which one respondent was pregnant and three were carriers. Multiple linear regression analysis shows that respondents who made an uninformed choice concerning the test had a significantly higher mean STAI score at Q2 compared to those who did not, corrected for other variables (Table 4). Of the respondents, 35 (26.5%) indicated they were worried while waiting for the test results. Two respondents indicated that they sought additional information about the relevant conditions while waiting for their partners test results, which increased their stress levels.

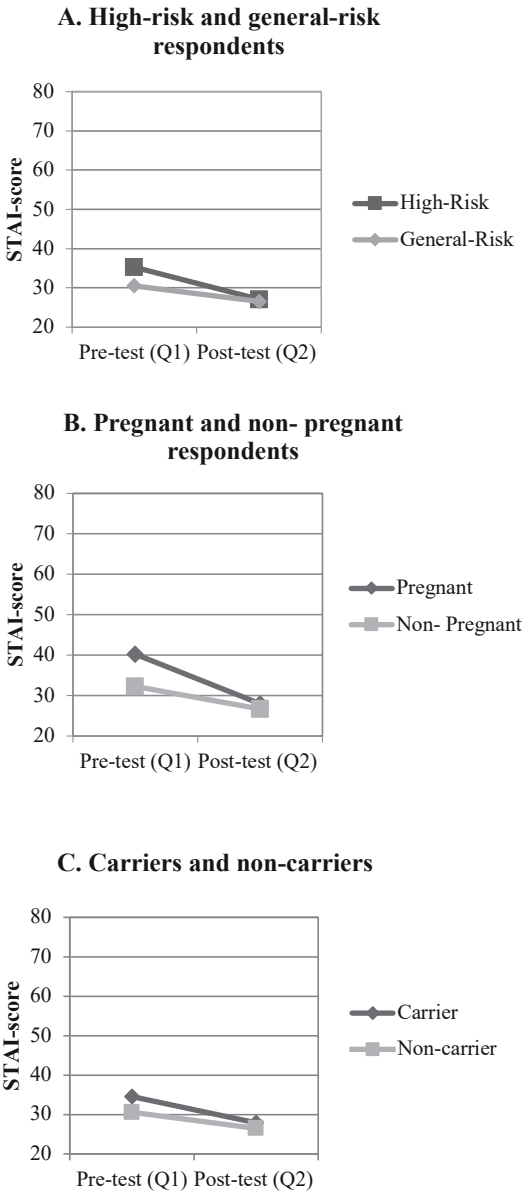

Figure 1. "Mean Spielberger State-Trait Anxiety Inventory (STAI) scores for different groups over time. STAI scores (range 20-80) before the test (Q1) and post-test results (Q2) for high-risk and general-risk respondents (A), pregnant and non-pregnant respondents (B), and for carriers and non-carriers/not tested respondents (C). A score ≥ 40 is considered as clinically significant.

Some interviewees reported that they felt relieved when receiving their, or their partner's, test results: *"When she said it was negative, I really felt such a big relief. I didn't even know I was so stressed about it. But it turned out that I was thinking about it a lot, unconsciously. Because I was so relieved when hearing my husband was not a carrier of CF."* (Woman, general-risk group, #2).

Distress at Q2 (IES-intrusion) was significantly higher for carriers compared to non-carriers, with a mean score 4.1 [SD 4.4] and 1.3 [SD 2.3] respectively ($p<0.0001$). Six of the 27 carriers and one non-carrier (who was pregnant) had clinically significant levels of distress [(>9) range 10-13]. Of these six carriers, three had affected children and one had a deceased child with a recessive disease. After receiving the test result (Q2) none of the respondents, including all carriers, reported that they felt less healthy.

Table. 4. Variables that correlate with higher STAI scores after the test result

Variables	β (95% CI)	p-value
A priori high risk[a]	1.857 (5.41--1.69)	0.914
Pregnant[b]	1.93 (-3.76-7.03)	0.368
Having children[c]	-1.47 (-5.47-2.53)	0.466
Sex[d]	-0.269 (-3.83-3.29)	0.881
Uninformed choice[e]	8.606 (1.12-16.08)	**0.025**
Carrier[f]	0.491 (-3.17-4.15)	0.791

[a] Adjusted for baseline score STAI (Q1)

[b] Adjusted for baseline score STAI (Q1) and being a priori high risk

[c] Adjusted for baseline score STAI (Q1), being a priori high risk and being pregnant

[d] Adjusted for baseline score STAI (Q1), being a priori high risk, being pregnant and having children

[e] Adjusted for baseline score STAI (Q1), being a priori high risk, being pregnant, having children and being male

[f] Adjusted for baseline score STAI (Q1), being a priori high risk, being pregnant, having children, being male and making an uninformed choice

Impact on reproductive intentions

At Q1, 114/132 (86.4%) respondents indicated that they would opt for PND if they turned out to be a carrier couple, 100/132 (75.8%) would consider termination of pregnancy if the child would be affected, and 105/132 (79.5%) would like to have more information concerning PGT. For 19/86 (22.1%) respondents, reproductive plans changed after receiving the test results (Q2): two respondents (one carrier and one non-carrier) had doubts about having another child, one respondent wanted more children, and 16 respondents said they were more determined

to have children. In the interviews, it was mentioned that the test could offer reassurance to start planning the pregnancy in case of a negative (favourable) result. *"He said: well we are both carriers of 0 diseases, then I said: do you realize what you said? We can start! [to conceive]."* (Woman, general-risk group, #11).

Satisfaction

All respondents indicated that they would have the test again, and 80.2% would recommend the test to others, 12.8% did not know if they would recommend it and 7% would not recommend it. Reasons not to recommend the test to others included 'I believe everyone should decide this themselves' and 'It is quite expensive so it depends on the financial situation of the person'. Almost half (49.6%) considered the costs of the test too high. Moreover, interviewees mentioned that a reason in favour of sequential testing was to save costs (potentially only one partner needs a test). Some interviewees believed that the high costs of the test could create inequality in access: *"I think it is good that the test [ECS] is available, however, you can ask yourself: is it not only available for people with sufficient resources? So, what exactly is the target group? People who are often highly educated and know that the test exists."* (Woman, high-risk group, #15). The reported waiting time for (combined) results was generally seven weeks; 43.0% (37/86) of the respondents considered the waiting time too long. This was similar for respondents who opted for sequential or parallel testing. The vast majority of respondents (n=114, 86.4%) considered it essential that people receive face-to-face pre-test counselling. Others believed that information can also be provided online (n=10, 7.6%) or with a leaflet (n=6, 4.5%). Moreover, interviewees indicated that narrative stories and experiences provided on the website could be informative for couples when deciding to have the test or not.

Discussion

This is one of the first studies to evaluate experiences with an ECS test in a non-commercial hospital setting from the perspective of test participants. Our results show that most participants made an informed choice, experienced no or limited negative impact on psychological well-being, and were satisfied with the test despite considering the cost of the test too high.

The most important reason for participants to have the test was to spare a future child a life with a severe hereditary disease. This is in line with previous survey studies assessing the hypothetical interest among potential users of ECS in the Netherlands [20,21]. However, in those studies, the second most important reason to opt for the test was to prepare yourself for having a child with a

severe disease [20,21], while in our study only 2.3% considered this an important reason. This difference could be explained by the relatively high number of high-risk couples in our study who might have already experienced the burden of having a child with one of the 50 disorders [31].

Previously, concerns were raised that the expansion of the number of disorders in the test-panels, in addition to the growing number of reproductive options, could undermine couples' informed decision making [2,32]. In our study, a high percentage (86%) of respondents made an informed choice, which could be the result of the extensive pre-test genetic counselling that was provided. In literature, informed choice for population reproductive genetic screening initiatives ranged from 27-51% [33]. This discrepancy could be due to the variety of contexts in which MMIC was measured, to differences in the definition "good knowledge" or differences in educational level which may be an explanation for the high levels of informed choice in this study. Most respondents in our study correctly recalled their test results. However, in line with other studies on single disorders [15] and smaller gene panels [23] respondents tended to misunderstand the implications of the residual risk of a screen-negative test, although the actual residual risks in general are low for the tested couples. This stresses the importance of adequate pre-and post-test counselling, as was mentioned before in the European Society of Human Genetics recommendations [2]. One possible solution to avoid information overload during counselling could be to offer generic consent. With generic consent, conditions and implications are explained more generally, such as the possibility to be carrier of a condition that is accompanied with a severe intellectual deficit, instead of counselling about all the possible conditions individually [34]. Moreover, when, in the future, ECS is offered as part of a population screening program, face-to-face pre-test counselling by clinical geneticists only, as was done in this study, is not likely to be feasible.

Overall, mean levels of anxiety were not clinically elevated. Anxiety levels were higher before than after ECS results, which is in line with previous studies for one disorder [15] or a smaller panel [23]. Pregnant participants had relatively higher anxiety levels, which was in accordance with a recent ECS study among pregnant and non-pregnant women in China, in which higher anxiety levels were reported for pregnant respondents (and their partners) [14]. This confirms that ECS should preferably be offered before instead of during pregnancy [2,35]. Moreover, our study shows that respondents who have made an informed choice had significantly lower levels of anxiety after testing, which emphasizes the importance of informed decision-making. Overall distress levels were not clinically significant, although for six carriers distress levels were high.

This supports the importance of post-test counselling, especially for people with positive family history, to provide guidance on future reproductive choice [11].

No new carrier couples were identified among the survey respondents. Some respondents expected that the ECS would help them decide about having children and indicated that their wish to have children became stronger after the test. A review on reproductive decision-making of couples at risk showed that most couples would opt for PGT or PND with possible pregnancy termination following their ECS result [19], similar to our data. Generally, respondents were satisfied with the test; all respondents indicated that they would do the test again and 80.2% would recommend the test to others, which is in line with a previous Dutch study in which satisfaction with CF carrier screening was assessed [36]. Almost half of the participants considered the costs of the test too high, even though it was reimbursed for the high-risk group. Earlier, it was shown that most individuals from the general public were prepared to pay €75 [21], and only 3% were willing to pay €500-1000 [20]. Attention should be paid to equal access when people have to pay for the test out-of-pocket, and reimbursement for those who cannot afford it should be considered [4]. Moreover, it would be interesting to investigate whether responses are different when the test would be offered free of charge.

There has been discussion in literature on whether it is better to give individual test results to couples, or couple-based test results where only results are disclosed if both partners are carriers for the same disorder (carrier couple). Although this study did not investigate respondents' preferences towards test disclosure, literature shows that users generally prefer full disclosure of individual test results over couple-based results [37,38]. A hypothetical survey study however showed that a majority of respondents had no objection towards receiving couple-results only .The latter is considered a more sustainable scenario in a public healthcare setting due to lower costs and workload [40]. Moreover, in order to avoid undue psychological impact, a couple-based approach could be more suitable [39].

Strengths and limitations

This study assessed the experiences of participants having an ECS test in a healthcare setting using a mixed methods design. Moreover, this study assessed perspectives of both high-risk groups and the general population. The results should, however, be interpreted with caution in terms of generalizability because the number of returned questionnaires after the test result was limited (n=86), and most of the participants were highly educated. Although ECS allows

testing regardless of risk, the majority of the participants in our study had a high a priori risk. This finding is similar to a study by Holtkamp et al. were an online direct-to-consumer test for CF intended for the general population, was evaluated and mainly used by people with a positive family history [41]. Another limitation is that there is no "gold standard" to measure informed choice [33], and couples' deliberation for testing was not assessed. Moreover, we do not know the reasons of test-decliners. No new carrier couples were identified among respondents, therefore the extent to which a positive carrier couple result impacts couples' psychological well-being and reproductive decision-making warrants further research.

Conclusion

This is one of the first studies to evaluate the experiences of participants with an expanded carrier screening test in a non-commercial setting. This study showed that both high-risk and general-risk participants were satisfied with having an expanded carrier screening test for 50 severe autosomal recessive disorders. Genetic counselling was regarded as valuable. However, waiting time for results was considered too long and costs of the test too high. To increase accessibility, out-of-pocket costs ideally should be reduced. The majority of respondents made an informed decision, suggesting that the counselling and information protocols at the AMC worked well for this highly educated group. Adverse impacts on psychological well-being were limited, although our findings support that offering ECS before - instead of during - pregnancy can avoid anxiety among pregnant couples. Moreover, some carriers showed distress which could possibly be minimized by only disclosing couple-based test results. The results of this study could be relevant for the implementation of initiatives on preconception expanded carrier screening.

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Supplement S1 Topics addressed in Questionnaire Q1 (pre-test) and Questionnaire Q2 (post-test)

Topic	Questionnaire	Question
Reasons to have the test (i)	Q1	What was the most important reason for having the carrier test? (tick one box from a list of 9 reasons with the option to add other reason)
Informed choice (ii):		
Uptake	Q1	Whether respondents agreed to have the test
Knowledge	Q1 and Q2	Eight knowledge questions, see Supplement S3
Attitude	Q1	Having the carrier test for 50 serious hereditary diseases for me is [Negative-Positive, Difficult- Easy, Frightening – Not- frightening, Reassuring – Not-reassuring (5-point semantic scale)
Recall and understanding of test results (iii)	Q2	Do you remember the results of the carrier test of you and your partner? (Each participant was asked to answer if they and/or their partner is a carrier and for which condition; not a carrier; had not been tested)
Psychological well-being (iv):		
Anxiety (STAI)[a][2]	Q1 and Q2	Six statements that evaluate how respondents feel "right now"/at this moment, such as I feel at ease, with four answer categories 1 = not at all, 2 = somewhat, 3 = moderately and 4 = very much so
Worry	Q2	-I was worried waiting for my test results. -I am worried now about the result of the carrier status test. (answer options: disagree, partly disagree, neutral, partly agree, agree)
Distress (IES)[b][3]	Q2	The occurrence of an event is scored as 1=not at all, 2=rarely, 3=sometimes, 4=often. Total of seven items, such as I thought about it without wanting to (subscale intrusion)

Supplement S1 Topics addressed in Questionnaire Q1 (pre-test) and Questionnaire Q2 (post-test) *Continued*

Topic	Questionnaire	Question
Health perception	Q2	I feel less healthy after hearing the test results (disagree, partly disagree, neutral, partly agree, agree)
Reproductive intention (v)	Q1 and Q2	- The results of the carrier test could help me in the future in making decisions about having children - I would not have (anymore) children if my partner and I were both carriers of the same condition - I would opt for prenatal diagnosis if my partner and I were both carriers of the same conditions - I would consider termination of pregnancy if the unborn child was affected with one of the 50 disorders - I would like more information about an IVF[c] treatment with embryo selection (pre-implantation genetic diagnosis), if I and my partner were both carriers of the same condition (All above questions had the following answer categories: disagree, partly disagree, neutral, partly agree, agree) -Did the test results change your ideas about having children? (Yes/No/ If yes, why?)

Supplement S1 Topics addressed in Questionnaire Q1 (pre-test) and Questionnaire Q2 (post-test) *Continued*

Topic	Questionnaire	Question
Satisfaction (vi)	Q1 and Q2	-If I had to decide again, I would participate again (If no, why not?) -Would you recommend the screening to other people? (Yes/No/I don't know) -I consider the costs of the test as too high (disagree, partly disagree, neutral, partly agree, agree) -I received sufficient answers to my questions during the information meeting. (disagree, partly disagree, neutral, partly agree, agree) - Do you think it is necessary that couples who want to have a carrier status test always have an interview first? (Yes: to check whether people understand enough, or to get people to ask questions, or because [...]. No: this is also only possible with a folder, or this is also possible with information online (via the internet), or because [...]. -I felt worried while waiting for the test result (disagree, partly disagree, neutral, partly agree, agree)

[a]STAI: Spielberger State-Trait Anxiety Inventory, [b]IES: Impact of Event Scale, [c]IVF: In vitro fertilization

Supplement S2 Interview guide

Topic list

Pre-test result experiences:
- General attitude toward genetic testing
- Application and information beforehand
- Expectations concerning test procedure
- Reasons to have the test

Counselling experience
- General views towards counselling
- Views on information provision

Waiting period and post-test result experience
- Impact of waiting time
- Communication of test result
- Meaning of test result
- Overall satisfaction

"Het water komt. Uit zee, van de bergen of uit de hemel. Het water valt onmogelijk tegen te houden. Wanneer we het water de vrije loop laten is het potentieel desastreus, maar wanneer we erin slagen het in banen te leiden en gecontroleerd over onze akkers te laten vloeien, is het een bron van leven en rijkdom."

- Pag. 228, Grand Hotel Europa van Ilja Leonard Pfeijffer

CHAPTER 5

Should germline genome editing be allowed? The effect of treatment characteristics on public acceptability

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Abstract

Study question: To what extent do characteristics of germline genome editing (GGE) determine whether the general public supports permitting the clinical use of GGE?

Summary answer: The risk that GGE would cause congenital abnormalities had the largest effect on support for allowing GGE, followed by effectiveness of GGE, while costs, the type of application (disease or enhancement), and the effect on child well-being had moderate effects.

What is known already: Scientific progress on GGE has increased the urgency of resolving whether and when clinical application of GGE may be ethically acceptable. Various expert bodies have suggested that the treatment characteristics will be key in determining whether GGE is acceptable. For example, GGE with *substantial risks* (e.g., 15% chance of a major congenital abnormality) may be acceptable to prevent a *severe disease* but not to *enhance* non-medical characteristics or traits of an otherwise healthy embryo (e.g., eye colour or perhaps in the future more complex traits like intelligence). While experts have called for public engagement, it is unclear whether the public acceptability of GGE is affected by the treatment characteristics proposed by experts.

Study design, size, duration: The vignette-based survey was disseminated in 2018 among 1857 members of the Dutch general public. An online research panel was used to recruit a sample representing the adult Dutch general public.

Participants/materials, setting, methods: A literature review identified the key treatment characteristics of GGE: the effect on the well-being of the future child, use for disease or enhancement, risks for the future child, effectiveness (here defined as the chance of a live birth, assuming that if the GGE was not successful, the embryo would not be transferred), cost, and availability of alternative treatments/procedures to prevent the genetic disease or provide enhancement (i.e. preimplantation genetic testing (PGT)), respectively. For each treatment characteristic, 2-3 levels were defined to realistically represent GGE and its current alternatives, donor gametes and ICSI with PGT. Twelve vignettes were created by fractional factorial design. A multinominal logit model assessed how much each treatment characteristic affected participants' choices.

Main results and the role of chance: The 1136 respondents (response rate 61%) were representative of the Dutch adult population in several demographics. Respondents were between 18 and 89 years of age. When no alternative treatment/procedure is available, the risk that GGE would cause (other) congenital abnormalities had the largest effect on whether the Dutch public supported allowing GGE (coefficient=-3.07), followed by effectiveness (coefficient=2.03).

Costs (covered by national insurance, coefficient=-1.14), the type of application (disease or enhancement; coefficient=-1.07), and the effect on child well-being (coefficient=0.97) had similar effects on whether GGE should be allowed. If an alternative treatment/procedure (e.g., PGT) was available, participants were not categorically opposed to GGE, however, they were strongly opposed to using GGE for enhancement (coefficient=-3.37). The general acceptability of GGE was higher than participants' willingness to personally use it ($p<0.001$). When participants considered whether they would personally use GGE, the type of application (disease or enhancement) was more important, whereas effectiveness and costs (covered by national insurance) were less important than when they considered whether GGE should be allowed. Participants who were male, younger, and had lower incomes were more likely to allow GGE when no alternative treatment/procedure is available.

Limitations, reasons for caution: Some (e.g., ethnic, religious) minorities were not well represented. To limit complexity, not all characteristics of GGE could be included (e.g., out-of-pocket costs), therefore, the views gathered from the vignettes reflect only the choices presented to the respondents. The non-included characteristics could be connected to and alter the importance of the studied characteristics. This would affect how closely the reported coefficients reflect 'real-life' importance.

Wider implications of the findings: This study is the first to quantify the substantial impact of GGE's effectiveness, costs (covered by national insurance), and effect on child well-being on whether the public considered GGE acceptable. In general, the participants were strikingly risk-averse, in that they weighed the risks of GGE more heavily than its benefits. Furthermore, although only a single study in one country, the results suggests that - if sufficiently safe and effective – the public may approve of using GGE (presumably combined with PGT) instead of solely PGT to prevent passing on a disease. The reported public views can serve as input for future consideration of the ethics and governance of GGE.

Introduction

In November 2018, a Chinese scientist claimed he had created the first genome-edited babies. The scientist had attempted to edit the C-C motif chemokine receptor 5 (CCR5) gene of several human embryos to introduce HIV resistance (Regalado, 2019). Three implanted embryos resulted in live births. This is an example of germline genome editing (GGE): directly modifying the DNA of embryos or germ cells, thereby introducing heritable changes. GGE is a form of germline gene therapy (GGT; the term 'gene therapy' is not meant to imply that any such experimental therapies will have therapeutic benefits).

Beyond this case, scientific progress has also been moving closer to clinical applications of GGE (Smith, et al., 2012). Several studies have reported successful GGE on human embryos without implantation (e.g.,(Liang, et al., 2015)). Furthermore, progress is being made in animal research, including in non-human primates (Ishii, 2015). Although increasingly successful, GGE is still considered insufficiently safe and effective for clinical application (NASEM, 2017). The scientific community thus overwhelmingly condemned the Chinese scientist's actions for violating research regulations and ethical norms, some even calling for a temporary global moratorium or ban (Adelman, et al., 2019, Botkin, 2020, Lander, et al., 2019). However, scientists expect that safety and effectiveness will improve, making clinical use of GGE feasible in the foreseeable future (NASEM, 2017, Smith, et al., 2012). GGE, however, raises various ethical questions (generally, GGE raises more ethical concern than somatic gene therapy, which does not result in heritable changes). The recent scientific developments have increased the urgency to resolve whether and when the potential clinical application of GGE may be considered ethically acceptable (Andorno, et al., 2020, Howard, et al., 2018, NASEM, 2017, NCOB, 2018, Ormond, et al., 2017).

Various influential bodies have concluded that clinical application of GGE may be acceptable under certain conditions (de Wert, et al., 2018, NASEM, 2017, NCOB, 2018, Ormond, et al., 2017). In addition to two consensus criteria, namely safety and effectiveness (Baltimore, et al., 2015, NASEM, 2017), several other conditions for clinical use have been proposed. Some have argued that GGT may only be used when no alternative treatment is available to prevent the disease (Green, 2008, NASEM, 2017). Other proposed criteria include that GGE should be sufficiently affordable (de Wert, et al., 2018), used to prevent diseases (not for enhancement, which raises additional ethical concerns (Knoppers, et al., 2018, NASEM, 2017)), and contribute significantly to the future child's well-being (Knoppers, et al., 2018, Smith, et al., 2012). Notably, these conditions do not

cover all ethical questions that GGE raises, including concerns about justice and eugenics (Andorno, et al., 2020, van Dijke, et al., 2018).

Many scholars have argued for public engagement (Andorno, et al., 2020, de Wert, et al., 2018, McCaughey, et al., 2019, NASEM, 2017, NCOB, 2018). Including the general public may improve the quality of governance decisions, encourage democratic deliberation about technologies with societal implications, and improve public trust in science (NCOB, 2018, Srinivas, 2017).

Several studies have since investigated public views. GGE acceptability varies considerably by case and between studies, ranging from 8-72% (Blendon, et al., 2016, Delhove, et al., 2020, Funk and Hefferon, 2018). These studies suggest that - at least for a significant part of the general public - the acceptability of GGE depends on certain conditions (Delhove, et al., 2020). The characteristics of GGT that affect acceptability among the general public seem similar to those identified by experts, including the treatments' safety (Robillard, et al., 2014, Wang, et al., 2017), effectiveness (Kalfoglou, et al., 2005), costs (Wang, et al., 2017, Xiang, et al., 2015), and whether alternative treatments are available (Hendriks, et al., 2018). Furthermore, acceptability depends on whether GGE is used for disease prevention or enhancement of specific characteristics/traits (Hendriks, et al., 2018) and how much GGE improves the future child's well-being (Funk, et al., 2016).

The existing literature, however, does not provide a comprehensive overview of the extent to which several treatment characteristics influence the acceptability of GGE. Several studies report importance ratings of GGT treatment characteristic(s) (e.g., reporting that safety is important (Wang, et al., 2017)). However, how these importance ratings translate into the acceptability of GGE with certain characteristics is unclear. Other studies do examine how a treatment characteristic affects the acceptability of GGE (e.g., reporting that GGE used for diseases is more acceptable than for enhancement (McCaughey, et al., 2019, Scheufele, et al., 2017)), but have significant limitations. The main impediment to understanding public views on actual cases is that existing studies have not taken into account that actual cases of GGE comprise various characteristics – both positive and negative (Delhove, et al., 2020). To determine the acceptability of a potential application of GGE, one needs to consider the relative importance of these characteristics and the trade-offs between them. For example, substantial risks may be acceptable if the prevented disease is severe, but not for less severe conditions. Disease applications may be more acceptable generally, yet enhancements with large benefits (e.g., longevity) may be more acceptable than preventing trivial diseases (e.g., inclination towards ingrown toenails). To

our knowledge, the simultaneous effects of multiple treatment characteristics on public acceptability of GGE have not been assessed.

This study examined the extent to which key treatment characteristics of GGE determine whether the Dutch general public supports permitting clinical use. As a secondary aim, the study explored whether the effects of the treatment characteristics changed if an alternative treatment would be available, or participants considered willingness to use instead of acceptability. Additionally, the study considered how much safer, more effective, or cheaper GGE should be, to counterbalance the negative effect of enhancement applications on acceptability. Finally, the study explored the perceived importance of potential societal effects and ethical arguments for or against GGE.

Materials and Methods

A vignette-based survey was developed, adhering to the International Society for Pharmacoeconomics and Outcomes Research criteria (Bridges, et al., 2011).

Selecting treatment characteristics and their levels

A systematic literature review and a public survey with open-ended questions were conducted to identify reasons (n=189) for or against clinical use of GGE which could be included as treatment characteristics in this study (Hendriks, et al., 2018, van Dijke, et al., 2018). However, vignettes with more than six characteristics are too complex (Ryan and Gerard, 2003), so the number of characteristics was limited using four strategies. First, reasons were excluded that were difficult to transform into treatment characteristics with quantifiable levels (e.g., GGE is too unnatural). Second, the most frequently reported reasons in the systematic review and qualitative study were shortlisted. Third, the relative importance of the shortlisted characteristics was reviewed based on comparative importance ratings from empirical studies and recommendations in conceptual papers (Supplementary Table SI). Finally, the treatment characteristics with the largest hypothesized impact on GGE acceptability were selected. Additionally, cost (covered by national health insurance, like most reproductive technologies in the Netherlands) was selected despite its mixed importance ratings, considering its importance for other reproductive treatments (Hendriks, et al., 2019). The final six characteristics included: 1) type of application (modifying an affected embryo to prevent the future child from having a disease or enhancing an embryo to provide the future child with a desirable characteristic); 2) effect of preventing the index disease or introducing the desirable characteristic on the future child's well-being; 3) risk that

the reproductive technology would cause major abnormalities (e.g., through off-target effects); 4) effectiveness (i.e., chance of a pregnancy that results in a live birth); 5) costs covered by national health insurance; and 6) availability of alternative treatments to prevent the future child from having the disease or alternative procedures to provide a desirable characteristic (e.g., preimplantation genetic testing (PGT)); Supplementary Table SII).

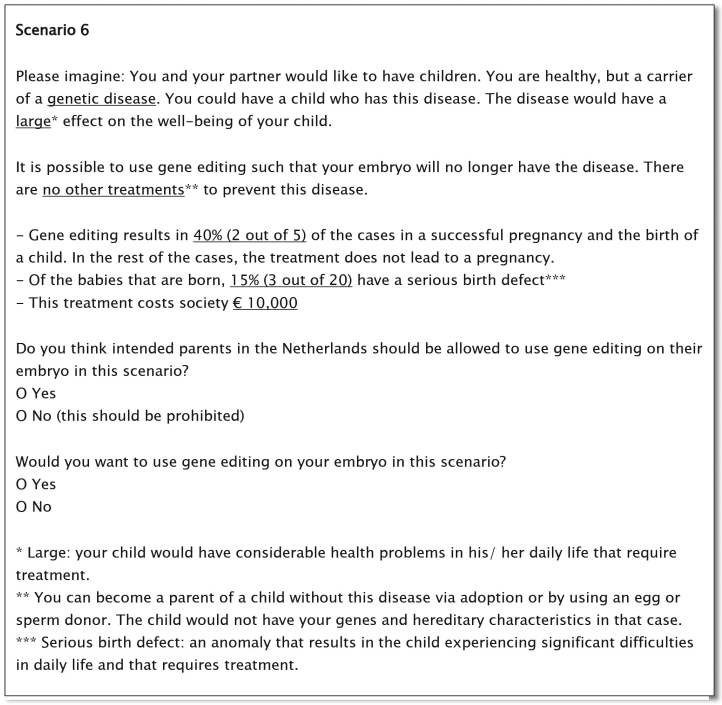
For effectiveness (characteristic 4), instead of narrow definitions of GGE effectiveness sometimes referred to in the literature (e.g., successful modification of cells or embryos), a broader definition was adapted: the chance of a live birth following the procedure (Duffy, et al., 2020) (assuming that if the modification would not be successful, the embryo would not be transferred). This allowed for comparison with PGT and referred to the most meaningful outcome for patients. Corresponding to the literature, alternative treatments/procedures (characteristic 6) were framed as options leading to genetic parenthood (NASEM, 2017). However, to avoid misconceptions (Andorno, et al., 2020), the vignettes in which no alternative treatment/procedure was available for couples' hypothetical embryos, noted that couples could still forgo genetic parenthood and use adoption or gamete donation to have child without the disease or with the desirable characteristic. Finally, throughout the paper, the word "procedure" is used to refer to enhancement, and "treatment" to refer to the prevention of a disease. We note that the Dutch survey used the Dutch word "behandeling" to refer to the prevention of a disease or the introduction of a desirable characteristic. While commonly translated to "treatment", "behandeling" is not necessarily connected to a medical condition. For example, it is commonly used to refer to cosmetic or wellness procedures.

For each treatment characteristic, 2-3 levels were defined to realistically represent GGE and its current alternatives, donor gametes and ICSI with PGT (Supplementary Table SII). As GGE is still in a preclinical stage of development, GGE levels were defined by expert judgment. Risk, effectiveness, and treatment costs were presumed to be evaluated relative to an alternative therapy, if available (Cavaliere, 2017, NCOB, 2018). Thus, when an alternative treatment/procedure was available, risks, effectiveness, and costs were described relative to the alternative (e.g., GGE is more, equally, or less expensive than the alternative). When no alternative treatment/procedure was available, these characteristics were described using absolute numbers (e.g., €5000, €10000, or €20000).

Survey design

The six treatment characteristics and their 2-3 levels resulted in 216 [2^3*3^3] possible hypothetical treatments. A fractional factorial design drew an efficient

sample of 12 vignettes (Ryan and Gerard, 2003). For each vignette, participants were asked whether Dutch couples should be allowed to use GGE and whether they would personally use GGE if the described scenario would apply to them (Fig. 1).



Scenario 6

Please imagine: You and your partner would like to have children. You are healthy, but a carrier of a genetic disease. You could have a child who has this disease. The disease would have a large* effect on the well-being of your child.

It is possible to use gene editing such that your embryo will no longer have the disease. There are no other treatments** to prevent this disease.

- Gene editing results in 40% (2 out of 5) of the cases in a successful pregnancy and the birth of a child. In the rest of the cases, the treatment does not lead to a pregnancy.
- Of the babies that are born, 15% (3 out of 20) have a serious birth defect***
- This treatment costs society € 10,000

Do you think intended parents in the Netherlands should be allowed to use gene editing on their embryo in this scenario?
O Yes
O No (this should be prohibited)

Would you want to use gene editing on your embryo in this scenario?
O Yes
O No

* Large: your child would have considerable health problems in his/ her daily life that require treatment.
** You can become a parent of a child without this disease via adoption or by using an egg or sperm donor. The child would not have your genes and hereditary characteristics in that case.
*** Serious birth defect: an anomaly that results in the child experiencing significant difficulties in daily life and that requires treatment.

Figure 1. Sample question from the survey. The combination of the description of the case ("scenario") and the questions about this case is referred to as a "vignette".

The survey introduction explained how GGE would work and current alternatives. Furthermore, the survey listed several ethical arguments for or against clinical use of GGE that were derived from the literature, which could not be transformed into treatment characteristics (e.g., GGE is too unnatural). Participants were requested to rate the importance of these arguments using a Likert scale. Finally, data on sociodemographic characteristics, engagement with biotechnology, trust in institutions, beliefs about nature and nurture, and the impact of genetic modification were collected (Gaskell, et al., 2006, Gaskell, et al., 2003, Singer, et al., 1998).

A science education expert edited the survey to lower its reading level. The survey was pilot tested and subsequently adapted to further improve understandability. Twenty-two cognitive interviews were conducted with a convenience

sample of the general public until three iterative interviews revealed no new issues. See the Supplementary data for the English translation of the survey.

Data collection

Public acceptability of prenatal gene therapy in the Netherlands is similar to other European Economic Area countries and the USA (Gaskell, et al., 2017). However, as limited public education has been a major limitation of previous studies (Blendon, et al., 2016), the Dutch public is interesting as they have the highest familiarity with gene therapy in the European Union (Gaskell, et al., 2006).

A sample of 1,857 members of the general public, matching specified demographic characteristics (i.e. gender, age, education, household composition, and region) of the Dutch adult population, was drawn from the online Flycatcher panel. Panel members (>10000) are invited to participate in ~10 surveys annually. The survey was disseminated in January 2018. One reminder was sent. Participants received points upon completion (approximate monetary value of €3).

Analysis

Analyses were performed using SPSS 24 (Armonk, NY: IBM Corp) and R (version 3.1.2; http://www.r-project.org). For the background variables, the proportions or measures of central tendency and variability were calculated.

The primary outcome was whether GGE should be allowed when no alternative is available. A main-effects multinominal logit model was used to determine how much each treatment characteristic and its levels affected participants' choices. All treatment characteristics were initially included as categorical variables. Risks, effectiveness, and costs were evaluated as continuous variables after confirming a linear relationship (determination was based on the Akaike information criterion). The output of the multinominal logit models included mean coefficients and their SDs, presented as 95% CIs.

The required amount of improvement in other treatment characteristics that would counterbalance the reduced acceptability of using GGE for enhancement (instead of for disease prevention) was calculated (i.e. marginal rate of substitution [MRS]). Of note, calculating improvements of other characteristics that would counter-balance the negative effect of enhancement on acceptability does not imply that the reasons why enhancement is less acceptable are related to these other characteristics. The MRS was calculated by dividing the difference in the importance scores between the highest and lowest treatment characteristic levels by the importance of GGE for enhancement, modelled as a continuous variable. The median and 95% CIs of the MRS were estimated through Monte

Carlo sampling and expressed as percentages (Berg, 2004). CIs were based on the Krinsky Robb method adjusted for class probabilities. Child well-being was excluded as this was a binary, categorical variable for which this analysis could yield no meaningful outcomes (i.e., it would yield a percentage of a large effect, as opposed to, for example, a percentage live birth rate).

Pre-planned multivariable analyses explored the associations of age, income, and gender with choices. Additional analyses explored the associations of the sociodemographic variables, the attitudes toward science, and the ethical arguments with the outcomes whether GGE should be allowed and willingness to use (when no alternative is available). These associations were only evaluated further when, based on univariate statistics, the variables were associated with preference at a p-value <0.15 to avoid overfitting.

Sample size calculations indicated that 280 participants were required for the main analyses. Larger samples allow for detecting effects of participants' sociodemographics.

Throughout the manuscript, participants' responses on whether Dutch couples should be allowed to use GGE, are referred to as public "acceptability" of GGE. "Acceptability" is thus a descriptive term —describing the survey results— but also has a normative component, since participants drew normative judgements about GGE cases. Normative reasoning by the public, may, however, be significantly different in nature than that by academics (Bærøe, 2020).

Ethical approval

Public surveys are exempt from ethical committee review in the Netherlands.

Results

Participants and their attitudes

The survey was completed by 1136 participants (response rate 61%). Table 1 presents the participants' sociodemographic characteristics and their attitudes toward science. Of the participants, 28% had a serious hereditary or genetic condition themselves, or had a family member or acquaintance with such a condition. The participants were representative of the adult Dutch general public regarding gender, region, educational level, and household composition, but were older (p=0.01, representing an 8-year difference in mean age). Figures 2 and 3 present participants' views on the importance of arguments for and against GGE. The most important arguments were the possibility of eradicating diseases (for) and the possibility of GGE being misused for profit (against).

Table 1 Sociodemographic characteristics of participants in a survey of the acceptability of germline genome editing and their attitudes toward science.

Sociodemographic characteristics		Proportion (%)
Male gender		576/1136 (50.7%)
Age (y)	18-44	419/1136 (36.9%)
	44-65	445/1136 (39.2%)
	>65	272/1136 (23.9%)
Western ethnic background [a]		1115/1136 (98.2%)
Education level	Low	335/1136 (29.5%)
	Middle	499/1136 (43.9%)
	High	302/1136 (26.6%)
Having children		740/1136 (65.1%)
Income	Minimum (less than €11,000)	67/1136 (5.9%)
	Below average (between €11,000 and €23,000)	229/1136 (20.1%)
	Modal (between €23,000 and €34,000)	239/1136 (21.0%)
	Between 1 and 2 times modal (between €34,000 and €56,000)	221/1136 (19.5%)
	Two times modal or more (€56,000 or more)	112/1136 (9.9%)
	Do not know / do not want to say	268/1136 (23.6%)
Type of religion	None	606/1114 (54.4%)
	Roman Catholic	240/1114 (21.5%)
	Protestant	183/1114 (16.4%)
	Other, including Islam, Hinduism, Buddhism	85/1114 (7.6%)
Importance of religion (mean ± SD; maximum importance is 10)		2.3 ± 3.2
Political preference [b]:	Left (1-4)	353/1036 (34.1%)
	Middle (5-6)	362/1036 (34.9%)
	Right (7-10)	321/1036 (31.0%)
Political preference [b]:	Progressive (1-4)	360/1053 (34.2%)
	Middle (5-6)	373/1053 (35.4%)
	Conservative (7-10)	320/1053 (30.4%)

Table 1 Sociodemographic characteristics of participants in a survey of the acceptability of germline genome editing and their attitudes toward science. *Continued*

Sociodemographic characteristics		Proportion (%)
The participant, or a family member or acquaintance of the participant has a serious hereditary or genetic condition		308/1100 (28.0%)
Self-reported knowledge about genetics	No knowledge	246/1136 (21.7%)
	Limited knowledge	726/1136 (63.9%)
	A fair amount of knowledge	134/1136 (11.8%)
	A lot of knowledge	30/1136 (2.6%)
Attitudes toward science		
Engagement with biotechnology [c] (mean ± SD, maximum score is 1)		0.37 ± 0.28
Nature versus nurture beliefs	Heredity and genes determine the behavior of a person as much as the environment and society in which a person grows up	706/1136 (62.1%)
	The environment and society in which a person grows up determine the behavior of a person most	271/1136 (23.9%)
	Heredity and genes determine the behavior of a person most	159/1136 (14.0%)
Trust in institutions	Physicians who are monitoring the health implications	915/1136 (80.5%)
	University scientists who are developing treatments	776/1136 (68.3%)
	Government institutions (e.g. National Institute for Public Health and the Environment) that are monitoring the health implications	649/1136 (57.1%)
	Ethics committees advising on the moral aspects	591/1136 (52.0%)
	The Dutch government in making regulations on the techniques	479/1136 (42.2%)
	The European Commission in making regulations on the techniques	374/1136 (32.9%)

Table 1 Sociodemographic characteristics of participants in a survey of the acceptability of germline genome editing and their attitudes toward science. *Continued*

Sociodemographic characteristics		Proportion (%)
	Media that are reporting on the techniques	203/1136 (17.9%)
	Scientists in industry who are developing treatments	195/1136 (17.2%)
	Spiritual / religious leaders advising on the moral aspects	147/1136 (12.9%)
Expected future impact of gene editing (in general)	Don't know	393/1136 (34.6%)
	It will improve people's lives	359/1136 (31.6%)
	It will worsen people's lives	202/1136 (17.8%)
	It will not affect people's lives	182/1136 (16.0%)

[a] Persons were defined as having a non-western ethnic background when they were born in a non-western country or at least one parent was born in a non-western country (https://www.cbs.nl/en-gb/our-services/methods/definitions?tab=m#id=migration-background).

[b] Participants were asked to place themselves on a 'political' scale of 0-10 (left-right and progressive-conservative), which were grouped into categories.

[c] A composite measure for engagement with biotechnology was created by adding 1) the frequency of discussing biotechnology, 2) the willingness to read articles or watch TV shows on biotechnology, and 3) the willingness to participate in biotechnology debates (Gaskell, et al., 2003). The composite variable was divided by 3 to get a score between 0-1, and described by mean and SD.

The effect of the treatment characteristics on GGE acceptability when no alternative treatment/procedure is available

Figure 4 uses coefficients to display the effect of each treatment characteristic on acceptability of GGE when no alternative treatment/procedure is available. The larger the coefficient, the larger the effect of this treatment characteristic on whether participants thought GGE should be allowed. If treatment characteristics increased the acceptance of GGE, their coefficients are positive. Negative coefficients reflect that treatment characteristics decreased the acceptance of GGE. The absolute values of the coefficients have no direct interpretation (Hauber, et al., 2016).

All treatment characteristics affected whether participants thought GGE should be allowed in the Netherlands. Participants were more likely to allow GGE when it was used to prevent diseases, it substantially benefitted child well-being, risks of causing congenital malformations were low, success rates were high and costs (covered by health insurance) were low.

Within their presumably realistic ranges, safety had the largest effect on whether participants thought GGE should be allowed, followed by effectiveness. Costs (covered by health insurance), the type of application (disease or

enhancement), and the effect on child well-being had similar, more moderate, effects on whether participants thought GGE should be allowed. Participants who were male, younger, and had lower incomes were more likely to allow GGE.

The effect of the treatment characteristics when considering willingness to use GGE or when an alternative treatment/procedure is available

There was a very strong positive relationship between participants' views on allowing GGE and their willingness to use GGE (Phi Coefficient 0.71-0.82; Supplementary Table SIII). However, GGE acceptability was higher than participants' willingness to personally use it ($p<0.001$). All treatment characteristics affected participants' willingness to use GGE if no alternative was available (Fig. 5a). Males and participants with lower incomes were more willing to use GGE. As compared to their effect on whether GGE should be allowed, the type of application (disease or enhancement) seemed to affect willingness to use GGE more, whereas effectiveness and costs (covered by national insurance) seemed to have less of an effect.

When the vignette described that an alternative treatment/procedure was available (and safety, effectiveness, and costs of GGE were described relative to the alternative), the effect of the treatment characteristics on the participants' support for GGE was different (Fig. 5b). Specifically, when an alternative procedure was available, participants were strongly opposed to using GGE for enhancement. The effect of the type of application (disease or enhancement) was so dominant to participants' (dis)approval of GGE, that the other treatment characteristics had only a limited effect. Only the effect on child well-being and effectiveness (compared to the alternative) also significantly impacted participants' choices. Supplementary Fig. SI displays the willingness to use GGE when an alternative treatment/procedure was available.

Associations with sociodemographic characteristics, attitudes toward science, or ethical arguments

Sociodemographic characteristics, attitudes towards science or the value participants attached to ethical arguments (Figs 2 and 3) were not associated with allowing GGE or willingness to use GGE, with one exception. Participants who considered uncertain long-term societal consequences important, were less likely to approve of GGE (coefficient 1.08, $p<0.01$) or use GGE (coefficient 1.13, $p<0.01$) when there was no alternative. As few participants had non-Western ethnic backgrounds, the effect of ethnicity was not assessed.

The necessary improvements in safety, effectiveness, or costs to compensate for the negative effect of enhancement

If two cases of GGE were identical in all characteristics (i.e. similar safety, effectiveness, costs, and effect on child well-being), but one prevented a disease and the other introduced an enhancement, the disease case would be more acceptable. However, MRS analysis showed that if, for example, the costs of the enhancement would be €13950 lower, both cases would be equally acceptable (95% CI: €8400-19500). Similarly, a 15.6% higher success rate or a 4.5% lower risk of major abnormalities would offset the reduced acceptability of GGE being used for enhancement instead of for disease prevention (95% CI: 10.5-20.6% and 2.10-6.8%, respectively). Notably, while acceptability may increase after compensating for the negative effect of enhancement, this does not necessarily mean a GGE case would be considered above the threshold of acceptability.

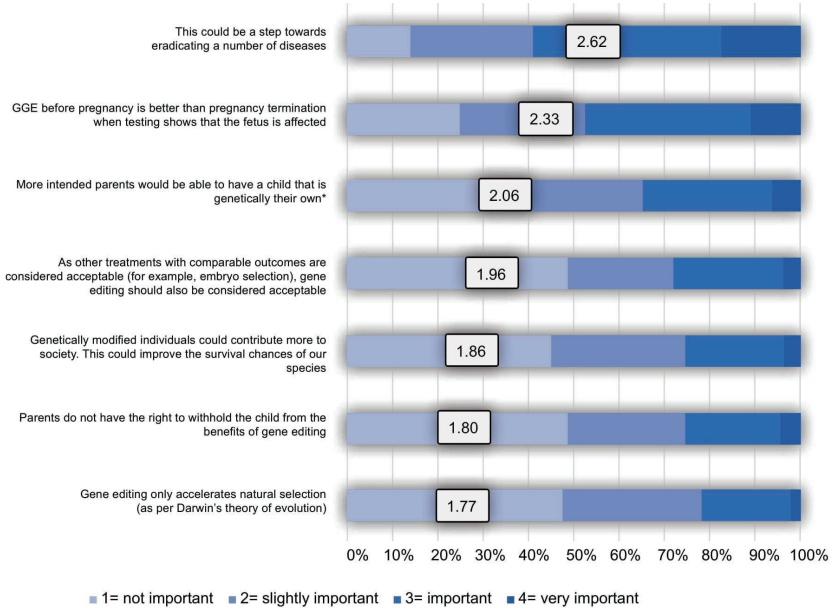


Figure 2. Importance of arguments for clinical use of GGE. Mean important scores are displayed in the white boxes on the bars. *A child that is conceived from the sperm and egg cell of his/her intended parents. The child thus has the genes and hereditary characteristics of his/her intended parents. GGE, germline genome editing.

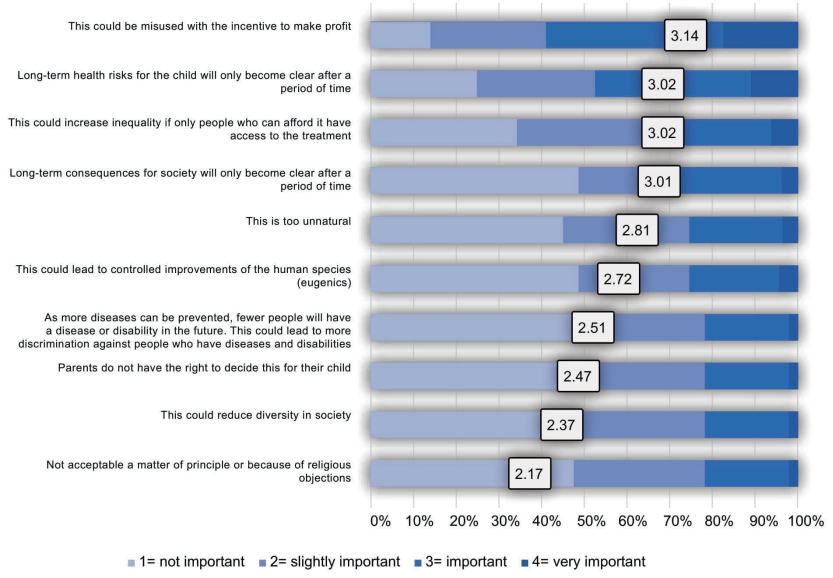


Figure 3. Importance of arguments against clinical use of GGE. Mean importance scores are displayed in the white boxes on the bars.

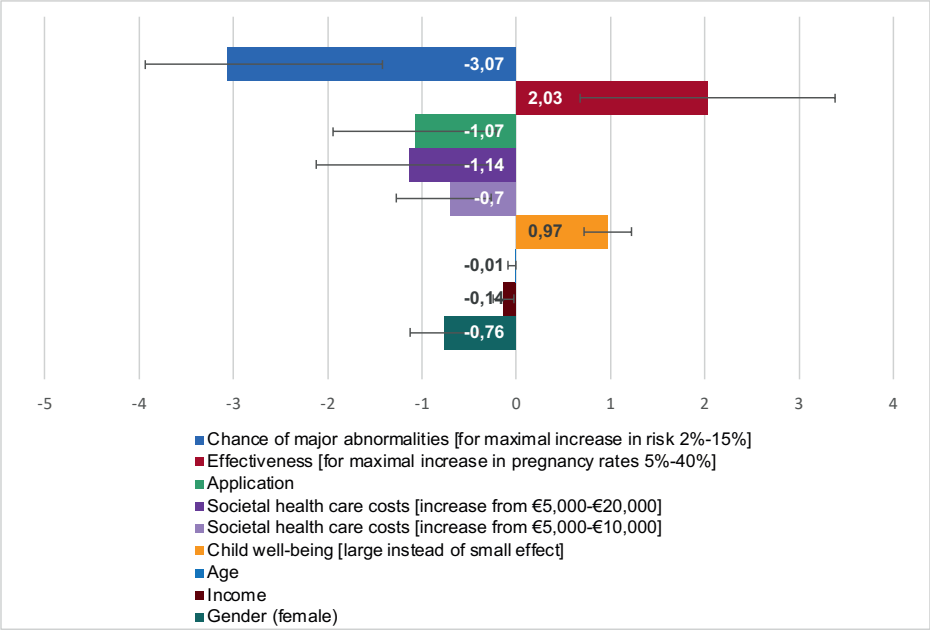


Figure 4. The effect of the treatment characteristics on whether participants thought GGE should be allowed in the Netherlands, when no alternative treatments/ procedures are available. Model parameters: 2 log-likelihood ¼ 542; Pseudo R2¼0.591; consistent Akaike Info Criterion ¼ 1183. *A translation of the linear variable. Coefficient per per cent increase in child safety 0.24 [CI: 0.37 to 0.10]. **A translation of the linear variable coefficient per per cent increase in effectiveness 0.06 [CI: 0.02 to 0.10].

Discussion

The results demonstrate that when no alternative for GGE was available, risks had the largest effect on whether the public supported allowing GGE, followed by effectiveness. Costs, the type of application, and the effect on child well-being had similar, more moderate effects on whether GGE should be allowed.

Strengths and limitations

To our knowledge, the simultaneous effects of multiple treatment characteristics on public acceptability of GGE have not previously been assessed. Existing literature focuses on importance ratings (e.g., (Wang, et al., 2017)) or on how *individual* treatment characteristics affect acceptability (e.g., (Scheufele, et al., 2017)). This study provides a more comprehensive and nuanced analysis of the effect that various treatment characteristics can have on GGE acceptability.

To enable investigating public views on a complex topic like GGE, several strategies were employed: providing information about GGE, using concrete vignettes (instead of abstract trade-off questions), employing a science education expert, and pilot-testing. While survey participants' understanding of complicated concepts is difficult to assess, the overlap between participant responses and expert views was encouraging. Furthermore, 87% of participants rated the survey's difficulty as easy to neutral. This study's participants were representative of the (Dutch) general public in multiple demographics, unlike many of the existing studies (e.g., (McCaughey, et al., 2019, Weisberg, et al., 2017)). Despite a good response rate (61%), some (e.g., ethnic, religious) minorities were underrepresented. Further research should assess additional perspectives. The latter may also include views of couples who are trying to conceive without passing on a genetic disorder. Their willingness to use GGE may differ from that of the general public who are imagining being in this situation.

To limit vignette complexity, only six treatment characteristics were included, consistent with accepted limitations of this methodology (Ryan and Gerard, 2003). However, the characteristics that were not included (e.g., out-of-pocket costs) may be connected to and alter the importance of the studied characteristics. This would affect how closely the reported coefficients reflect 'real-life' importance. Furthermore, as GGE is still being developed, the realistic ranges of levels of the characteristics were based on expert judgement, with some being further from current possibilities than others. Most notably, the combination of enhancement and GGE having a large effect on child well-being seems theoretically possible (e.g., with longevity as the enhancement) but far removed from current abilities and more uncertain and dependent on contextual factors (NCOB, 2018).

If alternatives to GGE were available, the risks, effectiveness, and costs levels were described relative to the alternative treatment/procedure, instead of using absolute numbers. While consistent with the literature (Cavaliere, 2017, NCOB, 2018), this limited the comparability of the scenarios and thereby assessment of the effect of alternatives being available.

Finally, the vignettes were selected using a theoretically efficient fractional factorial design. This design did not account for the dominance of the type of application in scenarios where an alternative was available, limiting detection of smaller effects of the other treatment characteristics.

Findings in the context of the literature

The acceptability (9-47%) and willingness to use GGE (6-38%) in this study's hypothetical scenarios were comparable to acceptability ranges in previous

studies on GGE 8-72% (Blendon, et al., 2016, Funk and Hefferon, 2018). GGE acceptability was higher than willingness to use although the two were correlated. While this was not previously assessed for GGE, similar results are reported for pediatric vaccines (Hadisoemarto and Castro, 2013).

The effect on child well-being, the type of application, safety, effectiveness, and costs all significantly affected GGE acceptability when no alternative was available. This validated their selection based on importance in the literature.

When no alternatives were available, risk of congenital abnormalities most affected acceptability and willingness to use GGE, a finding which corresponds to previous studies on GGT (Rabino, 2006, Wang, et al., 2017) and some experts' views (Smith, et al., 2012). Still, participants were strikingly risk-averse (Tversky and Kahneman, 1981) in that they weighed the risks of GGE more heavily than its benefits. For example, GGE use was more acceptable when it would cure a severe (rather than minor) disease. However, this positive effect was roughly nullified if GGE would increase the risk of a congenital abnormality by just 4% (extracted from Fig. 5). This was true even though major abnormalities and severe diseases were described as having similar effects on well-being. The appropriate policy implications of this risk aversion should be considered.

GGE's relative safety compared to available alternative treatments/procedures did not impact GGE approval. Based on the cognitive interviews, participants may have assumed that current treatments are low-risk (indeed, available data about ICSI with PGT is reassuring (Heijligers, et al., 2018)), such that increased safety will have little marginal utility. Moreover, participants may trust clinicians not to propose risky therapies when low-risk alternatives exist, such that when GGE was listed as riskier than the alternative, they presumed it not to be high-risk. Although safety may have had a small effect, the dominance of the type of application in the analysis prevented the detection of such effects. Further studies could compare GGE with riskier potential alternative therapies.

Effectiveness has only been reported as having a substantial impact on support for allowing GGT in qualitative data (in which effectiveness was not clearly defined, making comparison difficult) (Hendriks, et al., 2018, Kalfoglou, et al., 2005, Lewis, et al., 1997). However, the present study's finding aligns with public views on other reproductive therapies (Hendriks, et al., 2017) and general drug approval processes. While incorporating an effectiveness threshold could limit reproductive autonomy, such restrictions may protect patients from therapies with unfavourable risk-benefit ratios, and could be justified by public health insurance prioritizing cost-effective therapies (Riggan, et al., 2019). Interestingly, participants' support for allowing GGE increased if GGE was more effective than alternative treatments, providing an opening for couples to use GGE to

increase the number of available embryos after PGT. Around 2771 PGT cycles are annually registered by the European Society of Human Reproduction and Embryology for intended parents who are carriers of genetic disorders (including PGT for chromosome abnormalities, sexing for X-linked disease and single gene disorders from 71 centers) (De Rycke, et al., 2017). Potential use of GGE by these couples could substantially expand potential users beyond the small number of couples who are unable to create disease-free embryos (Viotti, et al., 2019) (which some experts proposed as a limit (Green, 2008, NASEM, 2017)).

GGE costs covered by public health insurance had a surprisingly large effect on whether participants supported allowing GGE, considering that in other studies the costs of GGT had mixed importance and insurance coverage was not always specified (Wang, et al., 2017, Xiang, et al., 2015). The results, however, resemble those for other reproductive treatments (Hendriks, et al., 2019) and may be understood in the context of a finite national healthcare budget and distributive justice concerns (Hui, et al., 2009, Wellcome Trust, 2005). Insurance-covered costs affected willingness to use less than acceptability. This might be because people are more likely to consider the treatment coverage's burden on the national healthcare budget when considering population-level introduction than when considering whether they would use such a treatment themselves. Self-interest may also play a role accepting costly treatments for themselves.

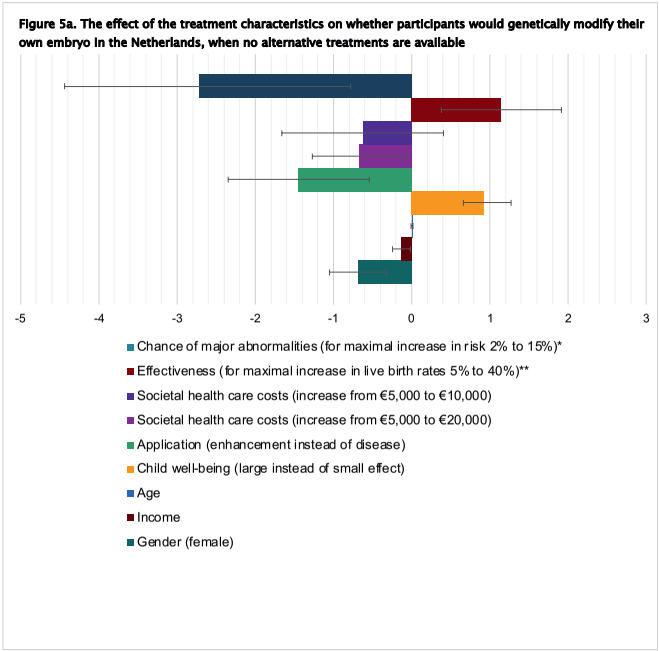
GGE acceptability was affected by the type of application (enhancement or disease) and the effect it would have on child well-being. Participants considered enhancements applications less acceptable than disease applications, even if the effect of both on the well-being of the child would be the same. An enhancement with a large effect on child well-being was considered almost as acceptable as a disease application with a small effect on child well-being. Participants thus disfavored enhancement, instead of merely judging both application types by their benefits (and risks), as some experts proposed (Green, 2008). Enhancement may be less acceptable in and of itself because of public concerns about its societal effects or ethics (e.g., justice) (Hendriks et al, 2018). When alternative procedures would be available that could provide couples with embryos with a desirable characteristic (e.g., PGT, theoretically), participants seemed to support expert statements that rule out using GGE for enhancement (NASEM, 2017, Ormond, et al., 2017). In the absence of alternative procedures, enhancement applications were still significantly less acceptable; however, this effect was not overwhelming relative to other undesirable treatment characteristics. This might indicate that, in this context, the public is slightly more tolerant of enhancement. Future research may explore this further.

The effect of GGE on child well-being was previously reported to be a key argument for GGT (Hendriks, et al., 2018, Robillard, et al., 2014). Furthermore, previous studies compared the acceptability of using GGE to prevent different diseases (e.g., HIV or a neuromuscular disease (Hendriks, et al., 2018)). However, because specific diseases differ in multiple ways, such comparisons do not reveal how the effect of GGE on child well-being influences GGE acceptability. While these previous studies did suggest that the effect on child well-being would likely influence GGE acceptability, to our knowledge, this study was the first to directly test – and confirm - this.

Similar to previous studies on GGT, being male was substantially associated with GGE acceptance (Criger and Fekken, 2013, Weisberg, et al., 2017) and being young was slightly associated with GGE acceptance (Weisberg, et al., 2017). The result that low-income participants more frequently accept GGE contrasts with a Chinese study on GGT (Wang, et al., 2017). Surprisingly, considering various previously reported associations (e.g., (Weisberg, et al., 2017, Wellcome Trust, 2005)), other background variables had no effects in this study. This may relate to these previously reported effects being application - and context - dependent (Scheufele, et al., 2017, Wellcome Trust, 2005). Alternatively, by using detailed vignettes about GGE, this study may have evaded some confounders, for example, that trust in institutions increases acceptance of biotechnologies by decreasing perceived risks and increasing perceived benefits (Siegrist, 2000). Uncertainty about societal consequences affected GGE acceptability more than specific potential societal consequences, corresponding to a low tolerance for uncertain long-term consequences of biotechnologies among the European public (Pardo, et al., 2002). Despite the importance participants attached to some of the other potential societal effects and ethical arguments for or against GGE (Figs 2 and 3), the importance scores of these ethical arguments had surprisingly limited effects on GGE acceptability in the vignettes. Further research may provide deeper insight into public views on these broader ethical arguments.

Implications

This study suggests that public support for allowing GGE is partially based on its risk-benefit profile as compared to an alternative treatment baseline, supporting previous qualitative findings on GGT (Wellcome Trust, 2005). This suggests that the general public conceptualizes GGE in a way that is consistent with several expert and committee position statements on GGE or GGT (Green, 2008, NASEM, 2017, Ormond, et al., 2017, Smith, et al., 2012). This in and of itself, as well as the relative importance of the different treatment characteristics to the public, provides input for future consideration of GGE ethics and policy.



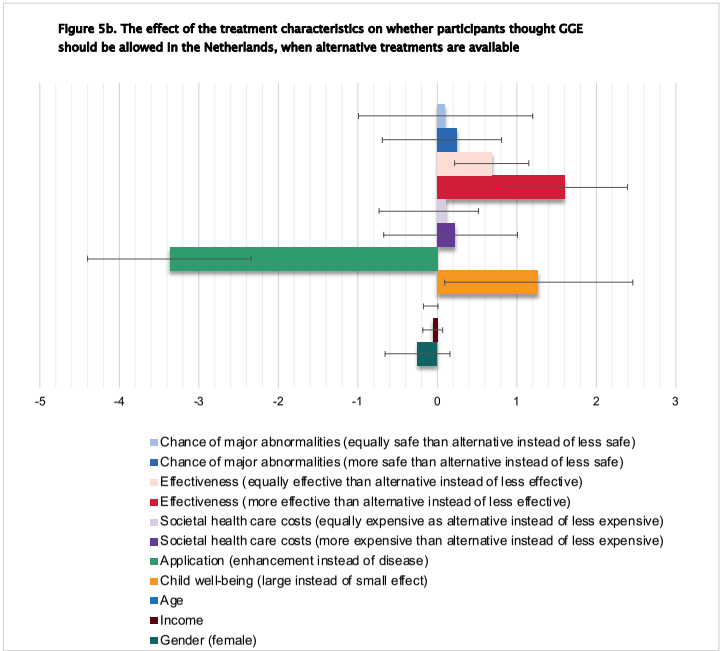


Figure 5. The effect of the treatment characteristics on willingness to use GGE when no alternatives are available and on GGE acceptability when alternative treatments/procedures are available. (a) The effect of the treatment characteristics on whether participants would genetically modify their own embryo, when no alternative treatments/procedures are available. Model parameters: 2 log-likelihood=-542; Pseudo R^2=0.591; consistent Akaike Info Criterion = 1183. If the 95% CI does not cross zero, the effect is significant at P<0.05. *A translation of the linear variable. Coefficient per per cent increase in child safety -0.21 [CI: -0.35 to -0.06]. **A translation of the linear variable. Coefficient per per cent increase in effectiveness 0.03 [CI: 0.01 to 0.05]. (b) The effect of the treatment characteristics on whether participants thought GGE should be allowed in the Netherlands, when alternative treatments/procedures are available. Model parameters: 2 log-likelihood =-637; Pseudo R^2=0.328; consistent Akaike Info Criterion = 1352. If the 95% CI does not cross zero, the effect is significant at P<0.05.

Additionally, areas in which participants diverged from expert views may justify further consideration and study, such as participants' increased approval of GGE when it would be more effective than current treatments. Finally, the results can inform the research agenda for developing GGE applications. Specifically, the increased risks, effectiveness and cost thresholds for accepting enhancement may help to determine when, if ever, the technology is sufficiently advanced to consider enhancement applications. Generally, GGE policy should take into consideration both expert perspectives including rigorous normative analysis and –given the societal interest – public views on the ethics of GGE.

Several areas require further research. First, cultural differences, patients' views, and the effects of other treatment characteristics on GGE acceptability should be explored. Second, further analysis should clarify whether using donor gametes or adoption (not leading to genetic parenthood) is a 'reasonable alternative' to GGE. Whereas the dominant view is that these are not 'reasonable alternatives' (NASEM, 2017), conceptual bioethics papers (e.g., (Hyun and Osborn, 2017)) and an empirical paper (Hendriks, et al., 2019) have challenged this. Finally, this study may serve as an example of the merits of the more comprehensive and nuanced public engagement necessary for other high-impact emerging technologies (Riggan, et al., 2019).

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Supplementary Table SI. Motivation for selected characteristics

Attribute	Relative importance based on the frequency of being reported	
	Systematic review reporting on a total of 169 reasons (van Dijke, et al., 2018)	**Survey among the Dutch general public reporting on a total of 114 reasons (Hendriks, et al., 2018)**
Safety for the future child	Safety risks for the child was the **second** most frequently reported reason for or against GGE (n=153)	Safety risks for the child was the **third** most frequently reported reason for or against GGE (n=275)
Effectiveness*	Effectiveness was the **fifth** most frequently mentioned reason for or against GGE (n=73)	Effectiveness was the **24th** most frequently mentioned reason for or against GGE (n=61)

In other quantitative or qualitative papers on GGT or gene therapy including that of the germline	Selection of committee statements and opinion papers reporting on the characteristic being key [i.e. more important than other characteristics] to GGE decision-making
In a survey among Chinese general public (n= 11,036), safety was among the most important arguments (Wang, et al., 2017) In a survey among the Canadian and US general public (n=467), safety was among the most important arguments (Robillard, et al., 2014) In a survey among US and EU genetics researchers (n=1560), safety was among the most important reasons against GGE (Rabino, 2006) In focus groups among US students (n=743) most groups mentioned the importance of safety (Lewis, et al., 1997) In a survey among the UK general public (n~700), safety was among the most important arguments (Wellcome Trust, 2005) In a survey among Chinese students (n= 579) safety was among the most frequent arguments (Xiang, et al., 2015) In a survey among the Slovene students (n~700), safety was among the most frequently mentioned arguments (Črne-Hladnik, et al., 2009) In focus groups among the US general public (n=181), safety was among the most important arguments (Kalfoglou, et al., 2005)	(Baltimore, et al., 2015, Chan, et al., 2015, de Wert, et al., 2018, Friedmann, et al., 2015, Green, 2008, Holm, 2019, Howard, et al., 2018, NASEM, 2017, Ormond, et al., 2017, Smith, et al., 2012)
In focus groups among US students (n=743) most groups mentioned the importance of effectiveness (Lewis, et al., 1997) In focus groups among the US general public (n=181), effectiveness was among the most important arguments (Kalfoglou, et al., 2005)	(Baltimore, et al., 2015, Cavaliere, 2017, Chan, et al., 2015, de Wert, et al., 2018, NASEM, 2017, Ormond, et al., 2017, Smith, et al., 2012)

Supplementary Table SI. Motivation for selected characteristics *Continued*

Attribute	Relative importance based on the frequency of being reported	
	Systematic review reporting on a total of 169 reasons (van Dijke, et al., 2018)	**Survey among the Dutch general public reporting on a total of 114 reasons (Hendriks, et al., 2018)**
Costs (covered by health care insurance)	Costs was the **thirteenth** most frequently reported reason for or against GGE (n=35)	Costs was **not** among the most frequently mentioned reason for or against GGE (n=8)
Type of application	The possibility of non-medical application was the **third** most reported reason for or against GGE (n=104)	The possibility of non-medical application was the **ninth** most reported reason for or against GGE (n=170)
Effect on well-being	The effect on the well-being of the child was the **most** frequently reported reason for or against GGE (n=169)	The effect on the well-being of the child was the **most** frequently reported reason for or against (n=1505)
Availability of alternatives	The existence of an alternative is the **eighth** most mentioned reason for or against GGE (n=56)	The existence of an alternative is the **second** most mentioned reason for or against GGE (n=585)

* Effectiveness is not uniformly defined in this literature.
GGT, germline gene therapy; GGE, germline genome editing

In other quantitative or qualitative papers on GGT or gene therapy including that of the germline	Selection of committee statements and opinion papers reporting on the characteristic being key [i.e. more important than other characteristics] to GGE decision-making
In a survey among Chinese public (n=11036), costs was among the most important arguments (Wang, et al., 2017) In a survey among US and EU genetics researchers (n=1560), costs are among the most important arguments (Rabino, 2006) In a survey among Chinese students (n= 579) costs was among the most frequent arguments (Xiang, et al., 2015)	(de Wert, et al., 2018, Ormond, et al., 2017, Smith, et al., 2012)
In a survey among US and EU genetics researchers (n=1560), the possibility of enhancement was among the most important arguments (Rabino, 2006) In focus groups among US students (n=743) most groups mentioned the importance of type of application (Lewis, et al., 1997) In a survey among the Australian general public (n=1507) the type of application was among the most important factors affecting support of GGE (Critchley, et al., 2018)	(NASEM, 2017, Ormond, et al., 2017)
In focus groups among the US general public (n=181), effect on well-being was among the most important arguments (Kalfoglou, et al., 2005) In a survey among the US general public (n= 4726), the effect on well-being was among the most important arguments (Funk, et al., 2016) In a survey among the Canadian and US general public (n=467), improving well-being was among the most important arguments (Robillard, et al., 2014) In a survey among the UK general public (n~700), improved on well-being was among the most important arguments (Wellcome Trust, 2005)	(Cavaliere, 2017, de Wert, et al., 2018, Howard, et al., 2018, NASEM, 2017, Smith, et al., 2012)
In a survey among US and EU genetics researchers (n=1560), the availability of alternatives was not among the most important arguments (Rabino, 2006) In focus groups among US students (n=743) most groups mentioned the importance of the availability of alternatives (Lewis, et al., 1997)	(de Wert, et al., 2018, Green, 2008, NASEM, 2017, Vassena, et al., 2016)

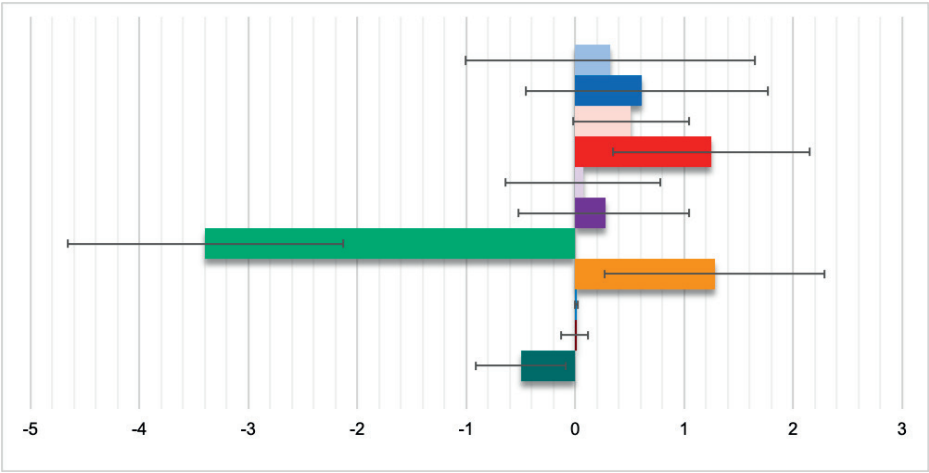
Supplementary Table SII. Treatment characteristics and levels

Treatment characteristics	Levels		
Type of application	Disease	Enhancement	
Effect on child well-being [a]	Large effect	Small effect	
Alternatives available to reach the same goal			
(i.e. a healthy child that is genetically their own)	Yes	No	
Chance of major congenital abnormalities [c] **(child safety)**			
If an alternative is available	Less safe than alternative	Equally safe	Safer than alternative
If an alternative is not available	2%	10%	15%
Chance of a pregnancy resulting in a live birth (effectiveness)			
If an alternative is available	Less effective than alternative	Equally effective	More effective than alternative
If an alternative is not available	5%	20%	40%
Costs (covered by health care insurance)			
If an alternative is available	Less costly than alternative	Equally costly	More costly than alternative
If an alternative is not available	€5,000	€10,000	€20,000

[a] The effect on child well-being was characterized in relation to whether the application was for disease or enhancement. More specifically:

- GGE preventing a disease with a small effect on wellbeing (i.e. limited health problems in the child's daily life and that do not require treatment) or large effect on wellbeing (i.e. considerable health problems in the child's daily life that require treatment), or
- GGE providing the child with a desirable characteristic with a small effect on well-being (i.e. limited effect on the child's fulfillment and happiness) or large effect on wellbeing (i.e. significant effect on the child's fulfillment and happiness).

[b] A major abnormality was defined as an abnormality that results in the child experiencing significant difficulties in daily life and requiring treatment



Chance of major abnormalities (equally safe as alternative instead of less safe)
Chance of major abnormalities (more safe than alternative instead of less safe)
Effectiveness (equally effective as alternative instead of less effective)
Effectiveness (more effective than alternative instead of less effective)
Societal health care costs (equally expensive as alternative instead of less expensive)
Societal health care costs (more expensive than alternative instead of less expensive)
Application (enhancement instead of disease)
Child well-being (large instead of small effect)
Age
Income
Gender (female)

Figure SI. The effect of the treatment characteristics when considering willingness to use GGE when alternative treatments/procedures are available. Model parameters: 2 log likelihood = – 637; Pseudo R2 = 0.328; consistent Akaike Info Criterion = 1352. If the 95% confidence interval does not cross zero, the effect is significant at P<0.05.

"Het kwade is sterker maar het goede is met meer”

-De meeste mensen deugen van Rutger Bregman

CHAPTER 6

The ethics of clinical applications of germline genome modification: a systematic review of reasons

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Abstract

Study question: What are the reasons for or against the future clinical application of germline genome modification (GGM)?

Summary answer: A total of 169 reasons were identified, including 90 reasons for and 79 reasons against future clinical application of GGM.

What is known already: GGM is still unsafe and insufficiently effective for clinical purposes. However, the progress made using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated system (Cas) has led scientists to expect to overcome the technical hurdles in the foreseeable future. This has invited a debate on the socio-ethical and legal implications and acceptability of clinical applications of GGM. However, an overview of the reasons presented in this debate is missing.

Study design, size, duration: MEDLINE was systematically searched for articles published between January 2011 and June 2016. Articles covering reasons for or against clinical application of intentional modification of the nuclear DNA of the germline were included.

Participants/materials, setting, methods: Two researchers independently extracted the reported reasons from the articles and grouped them into categories through content analysis.

Main results and the role of chance: The systematic search yielded 1179 articles and 180 articles were included. Most papers were written by professionals in ethics, (science) journalism, and biomedical sciences. Overall, 169 reasons were identified, including 90 reasons for, and 79 reasons against future clinical application of GGM. None of the included articles mentioned more than 60/169 reasons. The reasons could be categorised into: (i) quality of life of affected individuals; (ii) safety; (iii) effectiveness; (iv) existence of a clinical need or alternative; (v) costs; (vi) homo sapiens as a species (i.e. relating to effects on our species); (vii) social justice; (viii) potential for misuse; (ix) special interests exercising influence; (x) parental rights and duties; (xi) comparability to acceptable processes; (xii) rights of the unborn child; (xiii) human life and dignity. Considerations relating to the implementation processes and regulation were reported.

Limitations, reasons for caution: We cannot ensure completeness as reasons may have been omitted in the reviewed literature and our search was limited to MEDLINE and a 5-year time period.

Wider implications of the findings: Besides needing (pre)clinical studies on safety and effectiveness, authors call for a sound pre-implementation process. This overview of reasons may assist a thorough evaluation of the responsible introduction of GGM.

Introduction

The prospect of intentional modification of the human germline has been both a source of excitement and unease for decades. Although tools for genome modification have been available for some (zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs)), their technical limitations rendered considerations about clinical applications of germline genome modification (GGM) theoretical (Lunshof, 2016). However, the discovery of CRISPR-Cas9, for its specificity, efficiency, low-costs, and ease in use, has represented a major step forward from previously available engineering tools (Cong, et al., 2013, Jinek, et al., 2012). Five groups have recently reported GGM of (non-viable) human embryos (Fogarty, et al., 2017, Kang, et al., 2016, Liang, et al., 2015, Ma, et al., 2017, Tang, et al., 2017). These experiments revealed the techniques are still unsafe and insufficiently effective for clinical purposes. Our lack of understanding about e.g. gene interactions and possible unintended consequences causes particular concern (IBC, 2015). However, scientists expect to overcome these technical hurdles in the foreseeable future (Ishii, 2015, Lunshof, 2016, Olson, 2016, Smith, et al., 2012). Indeed, although questioned by some experts (Egli, et al., 2017), remarkable progress has been reported, including high on-target specificity without off-target effects; although half of the embryos still had the mutation and more studies are needed to ensure reproducibility and safety (Ma, et al., 2017).

Three types of applications of GGM have been described, some more contentious than others (Chan, et al., 2015). First, GGM could correct disease-causing gene(s), to prevent diseases such as cystic fibrosis (Schwank, et al., 2013). Mostly, GGM would then represent an alternative to current reproductive options, such as preimplementation genetic diagnosis (PGD), to prevent the considered disease in the future child (Bosley, et al., 2015). Second, GGM could introduce a modification that reduces the risk of acquiring diseases, such as HIV (Kang, et al., 2016). Third, GGM could introduce non-medical enhancements to improve the quality of life of the resulting child, such as increasing muscle mass (Proudfoot, et al., 2015).

Many authors and professional societies have called for a debate about the socio-ethical and legal implications before the technical limitations currently preventing clinical introduction are overcome (IBC, 2015, NAS, 2015, NAS, 2017). The result has been a fierce and ongoing debate at international conferences and in academic literature and popular media (Baltimore, et al., 2015, Bosley, et al., 2015, Lanphier, et al., 2015). Whereas some consider it our moral duty to alleviate suffering by eliminating diseases or even applying non-medical en-

hancements, others foresee apocalyptic scenarios including the destruction of humanity (Smith, et al., 2012). However, an overview of the reasons provided on both sides is missing. This paper aims to provide an overview of, and framework for, the reasons in favour and against applying GGM clinically.

Methods

A systematic review of reasons was performed, which is a model to systematically identify the reasons provided in the literature on a normative position, claim, or phenomenon (Strech and Sofaer, 2012). We followed PRISMA recommendations (Moher, et al., 2009).

Search strategy

MEDLINE was systematically searched; the search string is provided as supplemental data (Supplementary Information Full Search String). The reference lists of eligible articles were perused for additional articles.

Article selection

Articles published in English between January 2011 and June 2016 were eligible for inclusion, including all article types (e.g. opinion articles), except for original biological research. Articles covering intentional modification of the nuclear DNA of the germline (i.e. embryo, zygote, gametes or precursor cells of gametes) were eligible and included if they discussed reasons for or against clinical application. Two researchers (SH and LB) independently considered inclusion through screening titles, abstracts and if necessary, full-texts.

Meta-synthesis

Meta-synthesis, rather than meta-analysis was performed considering the type of data (Hendriks, et al., 2015). Two reviewers (SH and ID or LB) independently performed the data collection and analysis; discrepancies were discussed until meeting consensus.

Data extraction

Several steps were taken to structure the identified reasons. First, we distinguished between reasons for and against clinical application of GGM. We did not describe the extent to which the authors endorse the mentioned reasons. The reasons were inductively grouped into categories by content analysis. This included multiple readings, highlighting meaningful units, grouping meaningful units into categories, and comparing meaningful units between categories to

integrate the categories (Graneheim and Lundman, 2004, Hycner, 1985). Considerations regarding the implementation processes and regulation were also indexed. Per article, we reported the disciplines represented by the authors (as identified through their listed affiliations) and, if relevant, the type of study participants. Finally, as the first experiments of human GGM may have changed the nature of the debate (Mathews, et al., 2015), we used Fisher's exact tests to analyse differences in how frequent domains were reported before and after 2015.

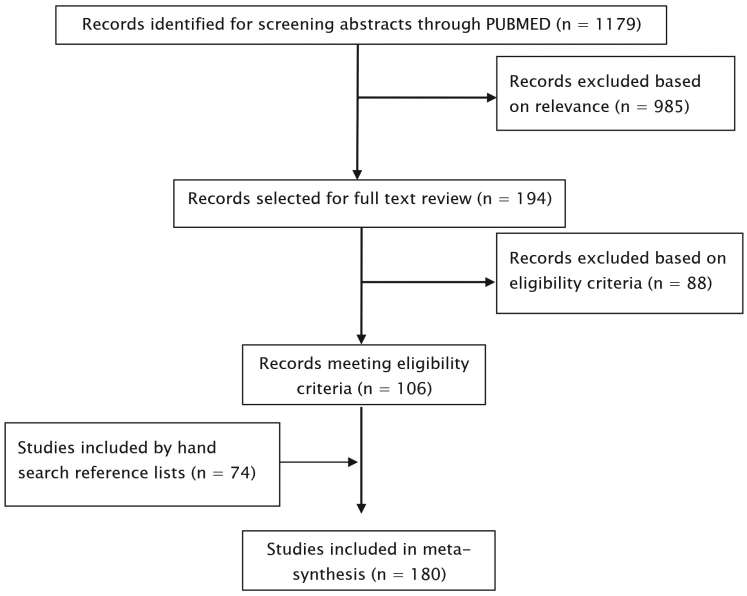

Figure I. Flowchart of the study selection process

Results

The systematic search yielded 1179 articles (Figure I). Based on eligibility, 106 articles were included. We found 74 additional articles perusing reference lists. In total 180 articles were included. Most articles were published in 2015 (n=120). 32 articles were published in 2011-2014; 28 between January and June of 2016. Represented stakeholders

The authors represented the following fields: ethics (n=64/180), (science) journalism (n=59/180), biomedical sciences (n=49/180), law/policy (n=22/180), social sciences (n=11/180), entrepreneurship (n=11/180), economics (n=2/84; Table I).

Table I. Stakeholder groups that have been used as sources (i.e. authors or study participants) in the articles

Stakeholder group	N	References[A, B]
Professionals in ethics	64	1-64
Professionals in (science) journalism	59	60,65-122
Professionals in biomedical sciences	49	1-3,5,8,16-18,23,26,28,30,32,41,44,56-58,60,62,123-151
Professionals in law and policy	22	2,4,5,8,14,15,24,25,29,44,54,56,60,64,133,152-158
Professionals listed as representing societies	19	5,8,19,23,131,159-172
Professionals in social sciences	11	9,29,62,130,156,173-178
Professionals in economics	2	152,153
Patient representatives (parents of children with genetic anomalies)	2	148,179
The general public	1	32
Professionals in (biomedical) entrepreneurship [C]	7	2,5,19,44,131,136,180
Number of stakeholder groups represented per paper		
Representing one stakeholder group	128	6,7,10-13,20-22,27,31,33-40,42,43,45-53,55,59,61,63,65-129,132,134,135,137-147,149-151,154,155,157,158,173-180
Representing ethics and biomedical sciences	12	1,3,16-18,23,26,28,30,41,57,58
Representing ethics and law and policy	7	4,14,15,24,25,54,64
Representing ethics and one other stakeholder group	2	9,19
Representing biomedical sciences and one stakeholder group	5	130,131,133,136,148
Representing law/policy and one other stakeholder group	3	152,153,156
Representing three or more stakeholder groups	9	2,5,8,29,32,44,56,60,62
Representing societies without specification of involved stakeholders	14	159-172

[A] As identified by the listed affiliation

[B] Numbers indicate the appropriate reference (see Supplementary data).

[C] Self-reporting representing a commercial company

A total of 19 articles represented (professional) societies. Parents of children with genetic diseases co-authored two articles. One article analysed an Internet forum on genome therapy. Most articles represented views of one stakeholder group (n=128/180). The most common collaboration was between ethicists and biomedical scientists (n=12/180).

Reasons for and against clinical application of GGM

We identified 169 reasons, including 90 reasons for, and 79 reasons against future clinical application of GGM (Table II). The articles reported a maximum of 60/169 reasons (Smith, et al., 2012). The reasons could be categorised into 13 domains (i) quality of life of affected individuals, (ii) safety, (iii) effectiveness, (iv) existence of a clinical need or alternative, (v) costs, (vi) homo sapiens as a species, (vii) social justice, (viii) potential for misuse, (ix) special interests, (x) parental rights and duties, (xi) comparability to acceptable processes, (xii) rights of the unborn child, (xiii) human life and dignity (Table II). Before 2015 (i.e. the first human GGM), three domains were mentioned more frequently: parental rights and duties (47% vs. 20%, p=0.003), comparability to acceptable processes (59% vs. 30%, p=0.002), and human life and dignity (47% vs. 30%, p=0.01) (Supplementary Table SI). The domains effectiveness (56% vs. 77%, p=0.03) and special interests (13% vs. 32%, p=0.03) were more frequently mentioned after 2015. Figure 2 displays the most frequently reported reasons per domain.

Should GGM be introduced in the clinic?

The most frequently reported reasons per domain

Reasons for	Reasons against
• Could prevent suffering of the child and the parents by curing a genetic disease • Could be a low-cost therapy by using CRISPR • Could reduce the frequency of diseases in the population • Could be considered unethical to withhold the child and/or society from access to this technique that relieves suffering • Could be accepted as achieving comparable outcomes through other means is also accepted	• Could pose safety risks for the child and subsequent generations due to off-target and on-target effects • Could be ineffective • Could meet only a small clinical need as there are almost always alternatives available • Could contribute to inequity within and between countries if access depends on wealth or other privileges • Could be misused by do-it-yourself-biologists • Could result in commercialization of the technology, potentially leading to exploitation • Could conflict with the principles of informed consent as there is no agent available to give consent • Could impinge on human dignity

Figure 2. The most frequently reported reasons per domain.

Quality of life of affected individuals

Seven reasons for GGM referred to improving the quality of life of affected individuals. GGM could prevent suffering of the child and the parents by curing

a genetic disease, prevent potential suffering of the child by reducing the risk of diseases, or improve the quality of life of the child and the parents by enhancing his/her non-medical traits. Articles argued GGM could provide progeny with an evolutionary advantage. Moreover, it could improve the job satisfaction of healthcare providers (as they care about their patients whose well-being is improved). Furthermore, it was argued GGM would have predictable effects on quality of life, and would not withhold parents from opportunities for guiding their children in overcoming difficulties.

In contrast, four arguments were raised that GGM, when successful, would not improve the quality of life of affected individuals. Specifically, despite reaching the desired outcome, GGM could cause discord in the parent-child relationship, hinder parents in supporting their child because of the large differences between them, withhold parents from guiding their children in overcoming difficulties, and could not have the expected positive effects on the quality of life of the child and/or the parents.

Safety

Overall, 18 arguments for GGM related to safety. Some articles discussed that GGM could be safe for the child by applying the following strategies: using CRISPR which is able to induce specific modifications, using preimplantation genetic screening (PGS) to assess off-target effects, reversing errors using the same technology, further development of the technique, modifying precursor gametes (which would build in natural checkpoints), and/or by introducing common genes of which unforeseen effects are unlikely. Additionally, articles reasoned that GGM could decrease the child's life-long treatment burden as he/she will not need further therapy or PGD to prevent passing on the disease to future offspring. Some argued that safety risks for the child could be justified based on the expected benefits for that child, or based on the overall benefits to mankind. The difficulty of determining acceptable levels of risk for the child was raised. It was suggested GGM could be more safe for the child than previously introduced techniques, sexual reproduction, or somatic genome modification. Additionally, it could allow couples to circumvent the maternal risks and psychological distress of pregnancy termination, the maternal risks and the burden of multiple IVF cycles for PGD and/or the maternal risks and the burden of IVF if in vitro-derived gametes are used.

Twelve concerns about safety were expressed. Articles argued that GGM could pose safety risks for the child and subsequent generations due to off-target and on-target effects (i.e. the targeted gene protecting against the targeted disease but increasing the risk on a different disease). Furthermore, it would

require using IVF, which by itself increases risks for the child. It could also result in the child suffering from psychological distress or social stigma. Concerns were expressed that the safety risks could be unpredictable and it could be difficult to ensure safety before clinical application or to assess safety by using PGS to assess off-target effects. Furthermore, ensuring the long-term follow-up required to assess safety could be challenging. Some reasoned that GGM could pose safety risks for the intended parents, the need for IVF would involve additional safety risks and burdens, and higher health risks for children would increase obstetric risks. Finally, some stressed that the process of developing GGM may expose people supplying research materials to risks.

Effectiveness

Six reasons for GGM related to effectiveness. Some articles argued that GGM could be effective, efficient, and easy to carry out by using CRISPR. Several authors stressed that effectiveness should be interpreted in the context of somatic genome modification, or current alternatives such as PGD, both of which may be less effective. Determining acceptable minimal limits of effectiveness could be challenging. Seven reasons against GGM related to effectiveness. It could be ineffective, inefficient, or difficult to carry out the techniques. Articles reasoned that GGM could be ineffective as causal mutations are in many cases unknown, many diseases/traits are too complex to modify, and many causal mutations arise de novo. Finally, some stressed that ensuring effectiveness through assessing mosaicism by PGS could be difficult.

Existence of a clinical need or alternative

Eight arguments in favour of GGM built on an unmet clinical need. Some articles discussed that GGM could meet an unmet need for obtaining genetic parenthood in case of certain parental genetic predispositions (e.g. both homozygous and therefore it would not be possible to select a not affected embryo), protecting against polygenic diseases, and introducing protective alleles that the parents do not have. Additionally, GGM could have unprecedented potential for eliminating heterozygous carriers from the population and improving the species with non-human traits. Finally, it could be preferable over current alternatives: by circumventing the creation of embryo's that will be destructed in PGD, by reducing the need for oocyte donors, and by preventing the ethical issues related to pregnancy termination.

Table II. Arguments in favour and against clinical applications of germline genome modification

Domain	Side	Argument	N	Reference[A]
uality of life of affected individuals	Positive	Could prevent suffering of the child and the parents by curing a genetic disease	169	1-8,10-44,46-51,53-62,64-95,97-132,134-137,139,140,142-150,152-172,174-176,178-180
		Could prevent potential suffering of the child by reducing the risk of diseases	29	13,15,17,23,28,34-36,41,43-45,58,60,61,67,100,108,117,120,125,129,131,144,145,158,160,161,163
		Could improve the quality of life of the child by enhancing his/her non-medical traits	104	1,3,6-10,12,13,15-20,23,26-29,31,32,34-37,39,41-48,50,51,53,55,58-60,63,64,67,68,70,72,73,76,77,79,81,83,85,88-90,95,98-100,103,105,106,108,111,115-120,124,125,127,128,130,131,133,136,138-146,154-158,160-165,171,176,178
		Could provide progeny with an evolutionary advantage	1	161
		Could improve the quality of life of healthcare providers by increasing their job satisfaction	1	38
		Could not prevent parents from all opportunities for guiding their children in overcoming difficulties	2	7,63
		Could have predictable effects on quality of life	1	59
	Negative	Could not have the expected positive effects on the quality of life of the child and/or the parents	17	6,9,10,31,35-37,45,46,51,58,59,64,91,95,117,146
		Could cause discord in the parent-child relationship	7	6,17,36,39,46,63,128

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could hinder parents in supporting their child as a result of the large differences between them	2	1,51
		Could withhold parents from guiding their children in overcoming difficulties	2	7,63
Safety	Positive	Could be safe for the child by using CRISPR which is able to induce specific modifications	43	3,14,16,23,28,37,38,43,48,55,60,62,70,76,77,79,81,89,90,93,95,100,104-106,108,110,113,117,119,121,122,124,137,145,146,151,155,162,163,170,178,180
		Could be safe for the child by using preimplantation genetic screening to assess off-target effects	13	1,2,17,28,35,43,44,57,60,121,125,131,139
		Could be safe for the child by reversing errors using the same technology	8	7,43,44,50,64,90,124,127
		Could be safe for the child by further development of the technique	4	38,43,89,117
		Could be safe for the child by modifying precursor gametes, which builds in natural checkpoints	2	43,139
		Could be safe for the child by introducing common genes of which unforeseen effects are unlikely	1	124
		Could decrease the life-long treatment burden of the child as he/she will not need further therapy	2	19,123

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could decrease the life-long treatment burden of the child as he/she will not need PGD to prevent passing on the disease to future offspring	2	34,44
		Could have safety risks for the child that are justified based on the expected benefits for that child	35	1,2,9,11,12,17,21,25,28,32,34-37,39,42,43,57,59,61,64,81,83,90,113,117,121,127,131,145,155,157,160,163,175
		Could have safety risks for the child that are justified based on the overall benefits to mankind	3	36,37,59
		Could have safety risks for the child of which acceptability would be difficult to determine	8	9,15,20,54,57,60,143,163
		Could be more safe for the child than previously introduced novel techniques	16	6,9,12,21,25,28,33-36,39,42,43,61,117,163
		Could be more safe for the child than sexual reproduction	17	9,11,12,20,39,43,56,61,64,72,85,113,124,139,157,163,175
		Could be more safe for the child than somatic genome modification	6	48,55,71,124,129,160
		Could allow couples to circumvent the maternal risks of terminating the pregnancy	1	38

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could allow couples to circumvent the psychological distress of terminating the pregnancy	3	38,134,139
		Could allow couples to circumvent the maternal risks and the burden of having multiple IVF cycles for PGD	1	38
		Could allow couples to circumvent the maternal risks and the burden of IVF if in vitro-derived gametes are used	2	35,134
	Negative	Could pose safety risks for the child and subsequent generations due to off-target and on-target effects	153	1-21,23-26,28-32,34-49,51,52,54-57,59-62,64,66-79,81,83-95,97-100,102,103,105-108,110,111,113-132,134-137,139-142,145-150,152,155-165,168,169,171-173,175,177-180
		Could increase risks for the child by requiring the use of IVF	1	141
		Could result in the child suffering from psychological distress	11	6,7,17,32,43,46,47,51-53,58
		Could result in the child suffering from a social stigma	2	35,131
		Could result in unpredictable safety risks for the child and subsequent generations	76	2,7-12,16-20,26,29,31,34-40,43,44,46,47,49,51,54,55,61,64,70-72,76,77,86-91,95,100,102,103,106,107,115-117,127,129-132,136,137,144,146,148,152,157,160,162-165,169,171,172,176-178,180
		Could be difficult to ensure safety before clinical application	13	8,17,28,35-37,39,47,51,55,117,152,177

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could be difficult to ensure safety by using preimplantation genetic screening to assess off-target effects	4	17,57,128,139
		Could be difficult to ensure the long-term follow-up required for assessing safety	9	1,8,17,28,40,60,79,127,164
		Could pose safety risks for the intended parents	4	58,60,134,160
		Could propose safety risks and burdens for the intended parents by requiring IVF	7	1,35,43,56,59,63,91
		Could increase maternal pregnancy risks by increasing risks for the child	1	56
		Could require a developmental process that exposes people who have supplied materials for research to risks	1	174
Effectiveness	Positive	Could be effective	16	2,8,17,18,35,37,43,55,93,100,105,106,121,126,142,150
		Could be efficient	28	1,4,14,16,17,23,26,28,38,40,48,55,57,60,64,95,102,104,136,137,139,145,149-151,162,163,165
		Could be easy to carry out by using CRISPR	60	2-4,17-19,23,28,40,44,48,50,55,57,60,62,67,68,71,72,76-79,81,83,87,89,90,92,93,95,98-100, 102,105,106,108,109,111,112,117,119,121,126,137,140,145,146,149,150,155,158,163,169-171,178,180
		Could be more effective than using somatic therapy	11	8,17,35,36,43,75,100,117,123,129,139
		Could be more effective than using current alternatives (e.g. PGD)	10	13,17,18,34,35,67,95,134,137,144

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could be difficult to determine acceptable levels of effectiveness	1	60
	Negative	Could be ineffective	73	1,2,4,8,10-13,15,17,19,23-25,29,32,35,38,40,41,44,45,47,48,50,57,60,62,70,71,73,74,77,81-83,86,87,90-92,94,97-100,102,103,106,107,110,113,115,118,122,124,127-129,131,133,137,139,148,150,152,159,160,162-165,175
		Could be inefficient	22	17,18,28,43,44,50,65,72,75,81,92,117,120,125,128,134,145,149,150,152,170,175
		Could be difficult to carry out the techniques	2	87,134
		Could be ineffective as causal mutations are in many cases unknown	22	26,28,35,44,48,56,64,85,86,91,98,100,108,117,134,139,141,145,151,155,156,163
		Could be ineffective as many diseases/ traits are too complex to modify	21	13,17,26,28,35,42,44,56,63,72,79,108,117,123,134,141,144,157,158,163,165
		Could be ineffective as many causal mutations arise de novo	2	26,163
		Could be difficult to ensure effectiveness by using preimplantation genetic screening to assess mosaicism	3	1,28,44
Existence of a clinical need or alternative	Positive	Could meet an unmet clinical need for obtaining genetic parenthood in case of certain parental genetic predispositions (i.e. inability to select not affected embryo)*	31	1,12,13,17,18,24,31,34,38,43,44,55,64,85,95,98-100,114,117,124,127,137,139,144,149,155,160,164,175,179

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could meet an unmet clinical need for obtaining genetic parenthood in case of protecting against polygenic disease (i.e. inability to select not affected embryo) *	4	28,34,35,43
		Could meet an unmet clinical need for obtaining genetic parenthood in case of introducing protective alleles that the parents do not have*	2	43,129
		Could have unprecedented potential for eliminating heterozygous carriers from the population	3	28,34,144
		Could have unprecedented potential for improving the species with non-human traits*	9	6,32,44,47,64,72,145,162,175
		Could be preferable over current alternatives by circumventing the creation of embryo's that will be destructed in PGD	12	28,34,55,66,85,98,100,127,129,134,139,155
		Could be preferable over current alternatives by reducing the need for oocyte donors	3	1,18,38
		Could be preferable over current alternatives by preventing the ethical issues related to termination of pregnancy	2	139,155

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
	Negative	Could meet only a small clinical need as there are almost always alternatives available	56	1,10,13,17-19,26,28,31,32,34,36,37,43,44,47,48,55,60,67,70-73,79,81,84,85,88,95,100,103,106,108,114,117,118,121,125,127,129,131,134,137,140,144,146,15-5,160,162-164,169,175,178,180
		Could create a demand that would not have existed without the existence of the technique	9	4,13,51,71,91,95,119,137,161
		Could be preferable over alternatives to only a limited number of people	1	155
Costs	Positive	Could be a low-cost therapy by using CRISPR	35	2,3,28,38,40,43,44,48,50,55,60,62,68,72,80,87,90,92,95,98-100,102,106,119,126,127,137,149,150,152,155,158,163,180
		Could be a low-cost therapy by improvements from further research	1	178
		Could be a low-cost therapy by commercialisation	1	55
		Could reduce health care costs for individuals and/or society caused by people living with the disorders	8	31,35,44,48,55,62,117,163
		Could allow people to contribute to society more economically	1	117
		Could create jobs in healthcare	1	24
		Could increase costs that are justified based on the benefits	1	174
	Negative	Could increase healthcare costs by being a high-cost therapy	7	1,10,17,44,117,136,148

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could increase healthcare costs by causing side-effects that require therapy	1	157
		Could increase healthcare costs by prolonging life	1	44
		Could lead to significant indirect costs for society through inciting large scale changes	2	10,136
		Could entail issues of distributive justice relating to investing in this rather than other issues	7	43,48,56,82,91,158,178
		Could increase medical tourism if there will be differences in costs	1	175
Homo sapiens as a species	Positive	Could reduce the frequency of diseases in the population	58	8,10-12,18,20,21,25,26,28,29,31,34-37,43,44,48,51,55,56,58,61,62,64,67,90,91,98,100-103,106,107,109,110,117,118,121-123,126,127,130,131,137,142,144,14-5,148,154,158,163,171,178,179
		Could allow modified individuals to contribute more to society	8	7,9,11,59,61,117,146,161
		Could safeguard the survival of our species by allowing modified individuals to contribute more	8	9,11,12,31,35,61,123,163
		Could have limited impact as consequences are restricted to individual and its descendants	4	20,21,64,157

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could be used for eugenics, however this is not necessarily morally wrong	9	7,35,42,58,146,156,161,163,178
		Could have large-scale consequences, however human resilience will likely prevent fall-outs	1	64
		Could have limited impact as widespread use is unlikely	5	10,28,35,44,91
		Could have limited effect on diversity as there are many traits	1	10
		Could have limited effect on the gene pool	4	21,28,35,44
		Could have no effect on the germline	1	124
		Could have no effect on future generations if modified individuals do not reproduce	1	157
		Could lead to a slippery slope, however this should not be a decisive argument against using this technology	6	34,35,43,103,116,124
		Could lead to worst-case scenarios, however this should not be a decisive argument against using this technology	7	10,24,34,51,60,103,157
	Negative	Could have potentially disastrous consequences leading to dystopias and the demise of our species	24	7,13,14,17,31,34,43,44,50,51,64,71,88,90,117,120,132,154,158,163,164,174,175,178

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could weaken the resilience of our species by reducing generational turnover through human life extension	1	31
		Could weaken the resilience of our species by reducing the diversity of the gene pool	5	6,10,32,44,64
		Could lead to eugenics	47	1,6,7,10,17,21,24,26,28,29,31,35,44,48,50,53,58,70,79,81,85,87,90,99,115-118,126,127,129,130,138,139,141,146,154,156,158,161,163-165,174-176,178
		Could incite a slippery slope towards unacceptable scenarios	31	2,13,16-19,31,34-36,41,43,44,51,68,69,71,76,81,89,99,102,116-118,127,131,133,138,175,178
		Could harm biodiversity and ecosystems	6	29,43,50,62,174,175
		Could alter cultural attitudes and values	10	31,35,44,49,50,53,58,128,138,152
		Could increase the medicalisation of reproduction	2	128,131
		Could incite a rat race	4	10,58,158,176
		Could reduce the valuable diversity in our society	6	6,10,32,42,91,179
		Could lead to social dilemmas	4	9,10,13,48
		Could have limited success in the elimination of diseases as this would require modifying heterozygous embryos	2	26,144
		Could have undesirable effects on society (unspecified)	11	32,47,83,85,91,103,126,131,136,160,171

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
Social justice	Positive	Could prevent the injustice of being dealt a poor genetic hand	6	35,43,45,55,62,64
		Could decrease segregation by providing disadvantaged groups with preferential access	1	7
		Could lead to equity and access to care issues, however this should not be a decisive argument against using this technology	5	7,21,43,60,154
		Could reduce the acceptability of disability, however this should not be a decisive argument against using this technology	1	35
		Could lead to generational inequity, however this should not be a decisive argument against using this technology	1	35
	Negative	Could contribute to inequity within and between countries if access depends on wealth or other privileges	45	
		Could contribute to inequity within and between countries through choices in the development of potential modifications	6	32,55,60,62,175,176
		Could create a 'genobility'	7	7,32,43,47,89,121,178
		Could lead to generational inequity	3	35-37

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could reduce the acceptability of disability	21	1,11,13,22,32,35,36,50,55,58,62,84,91,121,160,163-165,175,176,178
		Could contribute to inequity (unspecified)	6	10,36,37,50,121,175
Potential for misuse	Positive	Could pose no biosecurity risk	1	20
		Could be too complex to carry out for 'garage'-biologists	4	44,78,87,109
		Could be misused, however this should not be a decisive argument against using this technology	3	43,56,63
	Negative	Could pose a biosecurity risk	12	9,24,34,48,50,54,62,80,109,160,174,175
		Could be misused in ways that would be difficult to detect	1	55
		Could be misused by parents with wrong incentives	3	37,44,63
		Could be misused by do-it-yourself-biologists	17	23,40,44,48,68,78,80,83,87,99,102,109,112,116,126,175,180
		Could result in (governmental) coercion forcing people to use these technologies	11	10,21,32,35,37,59,77,127,162,164,178
		Could result in indirect coercion through social norms forcing people to use these technologies	6	21,35,44,55,62,91

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could result in indirect coercion through funding forcing people to use these technologies	4	35,91,127,163
		Could be misused (general)	16	1,17,18,34,49,50,52,56,86,106,121,125,127,143,157,163
Special interests	Positive Negative	Could incite commercial interests that are aligned with public interests	3	87,117,155
		Could result in commercialization of the technology, potentially leading to exploitation	38	4,35,41,48-50,54-56,62,75,87,88,90,92,100-102,105,106,111,115-119,121,127,131,138,149,156,158,160,161,163,175,176
		Could incite pressure from patients that leads to premature and/or inappropriate applications	11	3,50,54,56,60,62,72,112,156,161,163
		Could incite (commercial) interests of clinics that lead to premature and/or inappropriate applications	8	44,60,69,88,99,103,120,143
		Could incite (commercial) interests of researchers that lead to premature and/or inappropriate applications	8	60,75,90,99,107,142,158,165
		Could could incite special interest that have undue influence on policy-makers	2	62,156
Parental rights and duties	Positive	Could be considered part of parents' right of reproductive liberty	16	1,10,11,13,21,22,35-38,47,72,131,156,161,178
		Could improve reproductive autonomy	9	1,13,18,28,35,36,117,137,178

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
		Could constitute part of the parental duty to make decisions for their unborn child as he/she cannot yet make these	3	11,61,162
		Could result in irreversible negative outcomes when abstaining from its use	2	43,61
		Could be considered unethical to withhold the child and/or society from access to this technique that relieves suffering	32	4,7,10-12,22,23,31,34,35,37-39,43-48,51,59,61,64,87,91,117,129,154,158,161,174,178
	Negative	Could surpass the limits of reproductive liberty	5	6,10,22,40,131
		Could be considered part of parents' right of reproductive liberty, however this is not important	1	37
		Could make an appeal to the parental duty to protect child against uncertainties of experimental techniques	3	36,37,47
		Could make no appeal on a parental duty to perfect children as there is no such duty	3	35,37,59

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
Comparability to acceptable processes	Positive	Could be accepted as achieving comparable outcomes through other means is also accepted	33	6,7,9-12,17,20-22,33,36,38,40,43-46,50,55,58,59,61,63,72,90,91,117,139,145,156,161,178
		Could be considered natural as genes are modified in nature too	10	11,20,28,43,56,64,85,90,139,175
		Could be considered to meet the human drive to exercise control	6	7,17,26,63,117,178
		Could be considered as restoring nature	2	17,28
		Could be considered unnatural, however unnatural is not inherently wrong (i.e. naturalistic fallacy)	13	7,11,35,43,53,61,63,64,85,117,119,154,178
	Negative	Could intervene to an extent that only nature is allowed	26	6,7,12,13,17,31,32,35,37,49,53,55,62-64,99,115,117,118,141,155,161,162,164,177,178
		Could intervene to an extent that only God is allowed	13	6,7,12,13,17,43,48,51,56,64,100,155,161
		Could be considered unjustified as it is a preventive procedure	4	17,18,25,107
		Could be compared to accepted current practices, however these may also be unethical	1	46

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
Rights of the unborn child	Positive	Could implicate the non-identity problem	10	6,11,12,22,35,36,39,43,55,61
		Could lead to no relevant non-identity problem	4	22,35,43,55
		Could be done without implying that acceptance of a child is conditional	1	22
		Could leave the right to freedom of the child unaffected	6	6,22,36,44,45,58
		Could conflict with the principles of informed consent, however parents always make choices for their children	12	1,11,12,28,36,40,53,57,61,72,124,127
	Negative	Could impinge on the right to freedom of the child	17	7,12,36,40,43-48,52,53,58,72,130,160,175
		Could conflict with the principles of informed consent as there is no agent available to give consent	28	1,11,12,14,17,18,28,36,38,40,43,44,48,53,56,57,61,70,75,99,106,117,125,127,131,158,165,169
		Could conflict with the principles of informed consent as information about the technique is insufficiently available	6	3,32,36,40,127,176
		Could imply that the child is not unconditionally accepted	1	22

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
Human life and dignity	Positive	Could be congruent with societal values as the public will sympathise with disease carriers	6	1,51,84,91,117,175
		Could be congruent with religious values	6	7,12,32,63,161,175
		Could be congruent with human dignity as an embryo does not have a moral status	5	38,43,58,84,155
		Could be incongruent with some perceptions of human dignity but as long as what constitutes human dignity is unclear, this should not be a decisive argument against using this technology	6	22,38,39,53,60,165
		Could be opposed based on perceptions of a higher purpose of disease, however this should not be a decisive argument against using this technology as suffering serves no purpose	1	62
		Could incite a (temporary) yuk-response, however this should not be a decisive argument against using this technology	6	7,21,90,99,100,156
		Could incite religious objections, however this should not be a decisive argument against using this technology	3	43,82,121

Table II. Arguments in favour and against clinical applications of germline genome modification *Continued*

Domain	Side	Argument	N	Reference[A]
	Negative	Could impinge on human dignity	31	1,6,13-16,18,22,27,28,35,36,38,43,46,48,54,61,67,100,115-117,125,131,138,152,161,165,175,178
		Could conflict with the moral status of a human embryo, which implies they should not be modified and/or created for the purpose of research	22	1,13,17,18,22,23,28,34,39,41,43,53,55,58,60,84,155,160,161,163,165,175
		Could incite religious objections	13	20,32,43,44,63,64,82,116,129,138,155,165,175

A Numbers indicate the appropriate reference (see Supplementary data).

* Argument specific to germline genome modification

Three arguments against GGM referred to the clinical need being insufficient. Specifically, GGM could: meet only a limited clinical need as alternatives are almost always available, create a demand that otherwise would not have existed, and be preferable over alternatives to only few people.

Costs

Seven financial reasons were given for GGM. It could be a cheap therapy by using CRISPR, with improvements of further research, and by commercialization. Furthermore, curing children would prevent costs of (life-long) therapy and care for individuals and/or society, and would allow these individuals to contribute more economically. Additionally, it could create jobs in healthcare. Finally, some argued that the benefits justify the costs.

Six reasons against using GGM referred to costs. It could increase healthcare costs by: being an expensive therapy, causing side-effects that require therapy, and prolonging life. Additionally, it could lead to significant indirect costs for society through inciting large-scale changes (e.g. modifications increasing stature may require redesigning buildings to accommodate taller individuals). Furthermore, articles reasoned that investing in GGM rather than other issues (e.g. people currently suffering from these diseases) raises questions about distributive justice, and pricing differences may incite medical tourism.

Homo sapiens as a species

A total of 13 arguments in favour of GGM referred to benefits to our species. Articles suggested that GGM could reduce the frequency of, or eradicate, diseases in the population. It may allow modified individuals to contribute more to society and thereby even safeguard the survival of our species. Some argued that even potential eugenic purposes would not necessarily be unethical. Furthermore, although there may be large-scale consequences, human resilience will prevent fall-outs. Others reasoned negative impacts would be limited as consequences are restricted to the individuals and their descendants. Furthermore, some discussed that widespread use of GGM was unlikely, therefore limiting the potential societal impact. Specifically, effects on the gene pool and diversity would be limited as there are many traits. Additionally, GGM may not affect the germline (i.e. by modifying embryonic stem cells in ways that are not passed on to future generations) or may not affect future generations if modified individuals do not reproduce. Finally, some argued that the potential for worst-case scenarios or a slippery slope towards unacceptable scenarios are not limited to GGM and may be controlled, or otherwise should not constitute a decisive argument against GGM.

Overall, 13 concerns about GGM referred to our species. Some argued GGM could have disastrous consequences leading to dystopias and the demise of our species. For example, the resilience of our species could be weakened by reducing the gene pool's diversity and/or by reducing generational turnover through human life extension. Additionally, GGM could lead to eugenics, and to a slippery slope towards unacceptable scenarios. It may also harm biodiversity and ecosystems. GGM may alter cultural attitudes and values, increase the medicalisation of reproduction, and incite a rat race. It may lead to reducing valuable diversity in our society. Furthermore, it may present social dilemmas (i.e. a conflict between individual and collective interests). Additionally, some reasoned that eliminating diseases from the population would be unlikely as this would require large-scale modification of heterozygous embryos. Finally, some authors warn against unspecified undesirable societal effects.

Social justice

Five benefits of GGM in improving equality were named. It could prevent the injustice of being dealt a poor genetic hand, or even decrease segregation by providing disadvantaged groups with 'headstart' programmes or preferential access as a form of affirmative action. Alternatively, some argued that potential issues related to equity and access to care, reducing acceptability of disability, and creating generational inequity are not limited to GGM and may be controlled, or otherwise should not constitute a decisive argument against GGM. Six concerns about exacerbating issues relating to social justice were expressed. GGM could contribute to inequity within and between countries if access depends on wealth or other privilege, and/or through choices in the development of potential applications. It may create some form of a 'genobility' or lead to generational inequity (i.e. the first modified generation being disproportionally exposed to risks). Additionally, GGM may reduce the acceptability of disability. Finally, some warned against unspecified inequality issues.

Potential for misuse

Three arguments in favour of GGM related to its potential misuse. Articles reasoned that clinical application of GGM would not pose biosecurity risks, and misuse by do-it-yourself-biologists would be unlikely. Furthermore, the potential for misuse is not limited to GGM and may be controlled, hence it should not constitute a decisive argument against using GGM. Eight concerns about misuse of GGM were named. The potential for posing a biosecurity hazard and the difficulty to detect misuse of the technology were stressed. GGM could be misused by parents with wrong incentives and by do-it-yourself-biologists. The

potential for (governmental) coercion forcing people to use these technologies was addressed, as well as the potential for indirect coercion through social norms or funding. Finally, some warned against unspecified misuses.

Special interests

In favour of GGM, some authors referred to special interests. Specifically, they noted that commercial interests could be aligned with public interests in preventing the fall-out of potential harms. Five articles voiced concerns about exploitation by special interests. They argued that potential commercialization of GGM could lead to exploitation. Additionally, special interests/pressure from patients, clinics, and/or researchers may lead to premature or inappropriate applications. Finally, special interests could have undue influence on policy-makers.

Parental rights and duties

Five reasons for GGM related to parental rights and duties. Articles reasoned that using GGM is part of the intended parents' reproductive liberty, and would improve reproductive autonomy. Moreover, intended parents have a duty to make decisions about their unborn children and abstaining from GGM cannot be reversed. Finally, some considered it unethical to withhold the child and/or society from access to this technique to relieve suffering. Four concerns were raised relating to parental rights and duties. Some considered GGM to surpass the limits of intended parents' reproductive liberty. Others stated that even if part of parents' reproductive liberty, this right is not important. Furthermore, parents have a duty to protect their children against uncertainties of experimental techniques. Finally, some argued that there is no parental duty to have perfect children and, consequently, there is no duty to apply GGM.

Comparability to acceptable processes

Five reasons in favour of GGM drew comparisons to existing and accepted processes. Some articles reasoned that GGM could be accepted as achieving comparable outcomes through other means is also accepted. Furthermore, it could be considered: as natural, considering genes are modified in nature too; as meeting our human drive to exercise control; and as restoring the natural state. Finally, even if modification is considered unnatural, unnatural is not inherently wrong (i.e. naturalistic fallacy). Four concerns related to comparability of existing and accepted processes. These concerns included the arguments that only nature or God should intervene to the extent of GGM. Furthermore, some articles stressed that the intervention would take place before confirming the expression of the disease, and therefore could not be justified. Finally, some

reasoned that comparability to current practices is a flawed argument since these may also be unethical.

Rights of the child
The rights of the child were reflected in five reasons in favour of GGM. Some articles argued that considerations considering harm to the unborn child are irrelevant if the child would not have been born otherwise and would have a life worth living (the 'non-identity problem'). However, others explain the 'non-identity problem' may not be relevant here or does not provide a sound argument. Other articles reasoned that GGM would not impinge on the child's freedom, nor imply conditional acceptance of a child. Finally, some discussed that even if conflicting with informed consent, parents always make choices for their children and this should thus not be a decisive argument against GGM. Four worries were voiced about the rights of the child. GGM could impinge on the child's freedom (i.e. violate his/her right to an open future). Furthermore, it could conflict with informed consent as there is no agent available to give consent and as information about GGM is insufficiently available. Finally, using GGM may imply that the child is not unconditionally accepted.

Human life and dignity
Seven reasons in favour of GGM related to human life and dignity. Some argued that GGM may actually be congruent with: societal values, as the public will sympathise with disease carriers; human dignity, as embryos do not have a moral status; and religious values, as God enabled the use of this technology and modified individuals may serve God better. Alternatively, it was asserted that the following arguments should not be decisive against using this technology: arguments based on human dignity, since what constitutes human dignity remains unclear; the perception that suffering/disease has a higher purpose; a yuk-response (i.e. a negative emotional response); and/or religious objections. Three reasons against GGM related to human life and dignity. Articles reasoned that GGM would impinge on human dignity, and specifically, that human embryos should not be created or modified for the purpose of research, because that conflicts with the moral status of the embryo. Furthermore, religious objections were expressed.

Considerations regarding the implementation processes and regulation
Many authors expressed considerations regarding implementation processes and regulation (Table III). In determining acceptability, authors expressed the need to involve expert and non-expert stakeholders in an open discussion. Furthermore,

they argued that defining what medical conditions qualify for modification could be challenging. Additionally, defining the difference between: medical conditions and human variability (e.g. hearing loss), medical conditions and enhancement, human and non-human traits, and somatic and germline cells, may be difficult. Regarding regulation, some opposed setting up regulation as they argued intended parents and their clinicians/scientists should decide on acceptability. Some warned against overregulation, which may prevent proper research and debate and/or may incite unwarranted fears among the public. In contrast, many argued in favour of regulating GGM and referred to what they considered appropriate existing regulations, or the need for additional oversight. Some articles argued for regulating GGM to prevent a public outcry resulting in the prohibition of somatic genome modification. Some reasoned that regulation should be regional, to acknowledge cultural values. Others argued that it should be international, as regional choices would affect all countries, and having these regional differences would incite medical tourism. Articles discussed that regulation should be flexible to adapt to rapidly evolving technologies. Finally, concerns were expressed that enforcing regulations may be challenging in some countries, e.g. because they govern by guidelines or professional codes without effective enforcement mechanisms. Finally, some expressed unclarity about how and who ought to make regulatory decisions.

Table III. Considerations with regard to the implementation processes and appropriate regulation

Domain	Consideration	N	Reference[A]
Process of determining acceptability	There is a need to involve stakeholders in an open discussion, including experts as well as non-experts	93	2,4,5,8,11,13-15,17-19,21,23,26,29,32,38,41,44,48-50,52,54,55,60,62,67,70-72,74,77-82,84-88,90,91,94,96-98,100,102,103,107,112,116-118,120,121,126,128,131-134,137,139,142,143,145-148,152,153,155,158-165,167,168,170,171,173-177
	It may be difficult to define what medical conditions qualify for modification	31	1,2,15,17,23,31,32,44,55,58,60,62,64,72,74,88,89,95,101,105,117-119,126,136,143,158,160,161,163,173
	It may be difficult to define the difference between a medical condition and human variability	13	6,28,44,51,72,84,91,160,163,175,176,178,179
	It may be difficult to define the difference between a medical condition and enhancement	13	7,20,36,37,43,44,51,95,154,164,171,176,178
	It may be difficult to define the difference between human and non-human traits	1	158
	It may be difficult to define the difference between somatic and germline cells	1	49
Need for regulation	There is no need for regulation	4	10,12,99,174
	There is a need to prevent overregulation, which may prevent proper research and debate	5	14,24,44,97,124
	There is a need to prevent overregulation, which may incite unwarranted public fears	2	24,49

Table III. Considerations with regard to the implementation processes and appropriate regulation *Continued*

Domain	Consideration	N	Reference[A]
	There is a need for regulation	101	1,4,5,10-15,17-19,23,27-31,33-36,38,41,44,46,48-50,52,54,55,60,62,65-67,70,72,74,76,77,79,81-84,86-91,94,98-101,103,104,106,107,112-118,120,121,126-128,138,140,142,146,148,152,153,155-158,160,162-165,168-172,174,175,177-180
	There is a need for regulation to prevent a public outcry resulting in the prohibition of all applications of genome modification	24	3,17-19,41,44,54,62,67,71,72,76,79,83,87-89,91,97,100,103,127,133,173
	Regulation should be regional as it should acknowledge cultural values	11	20,44,60,77,81,84,95,136,155,157,160
	Regulation should be international as regional choices would have effects on all countries	19	1,23,48,50,62,70,76,81,88,89,96,112,142,157,160-163,165
	Regulation should be international as to prevent medical tourism	8	4,21,44,124,160,163,165,175
	Regulation should be flexible to keep up with rapidly evolving technologies	14	14,15,18,40,54,55,60,62,89,95,152,153,160,179
	It may be difficult to enforce regulation (in some countries)	41	1,3,7,14-17,20,21,23,38,44,48-50,55,60,62,65,71,72,76,80,83,85,87-89,97,101,107,113,114,117,124,126,127,156,161,163,178
	It may be difficult to define how and who should make decisions on regulation	19	21,23,26,28,32,49,55,62,81,112,113,115,131,152,153,160,161,164,177

A Numbers indicate the appropriate reference (see Supplementary data).

Discussion

This review provides, to our knowledge, the first systematic review on the ethics of GGM, identifying 90 reasons for, and 79 reasons against its future clinical application. Previous, non-systematic, articles presented a maximum of 60/169 reasons. This review represents a valuable addition to previous literature by providing an overview of, and framework for, the reasons put forward in this debate.

Limitations

There were several methodological challenges. First, different terminology is used and articles on GGM were poorly indexed, resulting in a broad search strategy and relying heavily on perusing reference lists. Second, unlike more traditional systematic reviews, we could not assess risk of bias in the included studies, as there are no quality criteria for performing a meta-analysis of opinion papers (Hendriks, et al., 2015). Third, synthesis required the reviewers to interpret the articles. Despite using two reviewers, the authors' meaning may have been misinterpreted. Additionally, we identified stakeholders' disciplines by their listed affiliations, which is a conservative interpretation of their expertise. Fourth, by systematically reviewing the literature, we aimed to provide a more complete overview of reasons. However, we cannot ensure completeness as relevant reasons may have been omitted in the reviewed literature (Strech and Sofaer, 2012). Moreover, the large volume of literature impelled us to limit the scope of our search for feasibility. Presuming that most arguments used in earlier debates, for example those in the seventies (incited by recombinant DNA technology), eighties, and nineties (incited by the Human Genome Project) have reappeared in the current discussions (Lunshof, 2016), we only included papers published between 2011 and 2016. We also excluded original biological studies, hoping to still cover insights from biomedical experts as they (co)authored n=53 non-biological studies. Additionally, our search was limited to MEDLINE, although we supplemented this by perusing reference-lists of identified papers. However, we acknowledge that these choices may have resulted in missing relevant reasons. Finally, to reduce the risk of bias, all reasons mentioned in the literature are described. However, neither describing reasons, nor reporting the frequencies of articles reporting on them, should be confused with a claim of which reasons are more sound, legitimate, or more important than others (Strech and Sofaer, 2012).

Findings in the context of literature

By summarising and quantifying the identified reasons, the results section served descriptive ethics. We provide some additional considerations.

At the core of many reasons for GGM is the importance of genetic parenthood. If genetic parenthood would not be as important, achieving the goals of GGM (i.e. preventing a genetic disease, reducing the risk of diseases and/or inducing non-medical enhancements in a future child) would be safer and more effective through e.g. selecting a suitable partner or sperm donor. Although infertile patients value genetic parenthood, they may not pursue it if that involves significant risks, costs, or limited success rates (Hendriks, et al., 2017, Hendriks, et al., 2018). Investigating the relative importance of genetic parenthood may be key in determining the value of GGM (Cohen, 2017, Hendriks, et al., 2018).

We differentiated between safety for the child and effectiveness. These differ when considering an embryo carrying a mutation as the starting point; i.e. effectiveness referring to the probability of curing the disease, and safety referring to not causing additional harm. However, for patients considering options for having healthy children, safety and effectiveness may be perceived as equivalent. Clarifying this may help communicating with the public.

Scholars have suggested that the reasons for and against GGM are not new, but have also been used for other novel technologies such as PGD (Harris, 2016, Tonkens, 2011). Indeed, we identified few reasons that are specific to GGM. These include improving the species with non-human traits and combining genetic parenthood with desired medical or non-medical traits that the intended parents cannot pass on. However, arguments being non-specific to GGM, does not diminish the need for reflection, as a difference in degree may be a difference in kind.

We found that effectiveness and special interests were more frequently mentioned after the first human GGM reports, which could relate to the experiments' low success rates. Special interests becoming a concern as some groups are actually working on GGM and fighting over securing patents (Ledford, 2017). Parental rights and duties, comparability to acceptable processes, and human life and dignity were discussed less frequently after the first experiments. We speculate that considerations about duties to perform GGM and its comparability to accepted practices is more relevant in theory and when the technique has advanced to being safe and effective. Furthermore, the experiments invited more accessible, but less in-depth, media attention.

Implications

Frameworks for evaluating ethical considerations of new technologies distinguish three steps: (i) identifying the relevant topics to consider, (ii) appraisal and analysis of the relevant topics, and (iii) decision-making on (conditions) for implementation (Assasi, et al., 2014).

This review contributes to the first step by providing an overview of the previously identified topics. However, our results also show that this first step is not saturated as non-expert perspectives are called for but insufficiently studied (Baltimore, et al., 2015, Chan, et al., 2015). Further research may identify novel reasons/topics by focusing on public and patients' perspectives. The domains identified here may present a framework for gathering and classifying new topics.

Additionally, future research may provide input for the second step by appraising the identified topics/reasons. Although all identified reasons deserve consideration, extra attention may be drawn to those where authors disagreed upon (e.g. whether the potential for a slippery slope should constitute a reason not introduce GGM), issues authors flagged as unresolved and challenging (e.g. defining the difference between medical conditions and enhancements), and the underlying values and concepts (e.g. obtaining genetic parenthood). This may involve both normative analysis and stakeholder consultation (Assasi, et al., 2014).

Regarding the third step, the decision-making on the introduction of GGM, we found that most articles stressed the need for regulation (Bosley, et al., 2015, Chan, et al., 2015). This corresponds to a broader plea for regulating novel techniques (Dondorp and de Wert, 2011, Schatten, 2002, Strasberg and Ludbrook, 2003). The current regulatory landscape covering GGM is diverse and complex (Isasi, et al., 2016, Isasi and Knoppers, 2015). Indeed, authors stressed that the appropriate regulatory process remains unclear (Lunshof, 2016). As such, we recommend further analysis of the regulatory process, including aspects raised by the articles such as the decision-making approach itself, the level of decision-making (i.e. international or national), ways of operationalising the requested regulatory flexibility, and maintaining public trust.

Conclusions

Besides needing (pre)clinical studies on safety and effectiveness, authors call for further ethical analysis and societal debate to define principles and conditions for responsible clinical use of GGM. This overview of the reasons may assist such a thorough evaluation.

Table IV All included articles by reference number as listed in Tables I–III and Supplementary Information Table S1.

1 = Araki and Ishii, 2014	61 = Harris, 2015b	121 = Economist, 2015a
2 = Baltimore et al., 2015	62 = Jasanoff et al., 2015	122 = Economist, 2015b
3 = Caplan et al., 2015	63 = Kahane, 2011	123 = Ayala, 2015
4 = Charo, 2016	64 = Powell and Buchanan, 2011	124 = Church, 2015
5 = Daley et al., 2016	65 = Callaway, 2016	125 = Deleidi and Yu, 2016
6 = Delaney, 2011	66 = Cressey and Cyranoski, 2015	126 = Doudna, 2015b
7 = Glick, 2011	67 = Cyranoski, 2015b	127 = Evitt et al., 2015
8 = Friedmann et al., 2015	68 = Cyranoski and Reardon, 2015b	128 = Flotte, 2015
9 = Gunson and McLachlan, 2013	69 = Cyranoski, 2015a	129 = Jacobs, 2013
10 = Gyngell and Douglas, 2015	70 = Lancet, 2015	130 = Krishan et al., 2016
11 = Harris, 2015a	71 = Gross, 2015	131 = Lander, 2015a
12 = Harris, 2016	72 = Hampton, 2016	132 = Lipsitch et al., 2015
13 = Hildt, 2016	73 = Kaiser and Normile, 2015	133 = Martikainen and Pedersen, 2015
14 = Isasi and Knoppers, 2015	74 = Kmietowicz, 2015	134 = Mulder et al., 2016
15 = Isasi et al., 2016	75 = Ledford, 2015d	135 = Yang, 2015
16 = Ishii, 2014	76 = Ledford, 2015c	136 = Wirth et al., 2013
17 = Ishii, 2017	77 = McCarthy, 2015	137 = Pergament, 2016
18 = Ishii, 2015	78 = Nature, 2016a	138 = Pollack, 2015
19 = Lanphier et al., 2015	79 = Nature, 2015b	139 = Porteus and Dann, 2015
20 = Lunshof, 2015	80 = Nature, 2016b	140 = Savic and Schwank, 2016
21 = Lunshof, 2016	81 = Nature, 2015c	141 = Rivera, 2013
22 = Malek, 2013	82 = Nature, 2015a	142 = Doudna, 2015a
23 = Mathews et al., 2015	83 = Vogel, 2015	143 = Baltimore, 2015
24 = Miller, 2015b	84 = Reardon, 2015c	144 = Lander, 2015b
25 = Miller, 2015a	85 = Travis, 2015	145 = Lovell-Badge, 2015
26 = Morange, 2015	86 = Tauxe, 2015	146 = Baltimore and Berg, 2015
27 = Walters, 2012	87 = Sheridan, 2015	147 = Cathomen and Ehl, 2014
28 = Vassena et al., 2016	88 = Senior, 2015	148 = Ellis and Terry, 2015
29 = O'Keefe et al., 2015	89 = Ledford, 2015e	149 = Kim and Kim, 2014
30 = Palpant and Dudzinski, 2013	90 = Specter, 2015	150 = LaFountaine et al., 2015
31 = Reagan, 2015	91 = Hayden, 2016	151 = Rajewsky and Delbruck, 2015
32 = Robillard et al., 2013	92 = Ledford, 2015b	152 = Addison and Taylor-Alexander, 2015a
33 = Savulescu et al., 2015a	93 = Ledford, 2016	153 = Addison and Taylor-Alexander, 2015b
34 = Savulescu et al., 2015b	94 = Maron, 2015a	154 = Casal, 2013
35 = Powell, 2015	95 = Maron, 2015b	155 = Greely, 2015
36 = Tonkens, 2011a	96 = Reardon, 2015d	156 = Kevles, 2015

Table IV All included articles by reference number as listed in Tables I–III and Supplementary Information Table S1. *Continued*

37 = Tonkens, 2011b	97 = Reardon, 2015b	157 = Evans, 2015
38 = Sugarman, 2015	98 = American, 2015	158 = Williams, 2015
39 = Sparrow, 2014	99 = Brown, 2015	159 = Dzau and Cicerone, 2015
40 = Smolenski, 2015	100 = Corbyn, 2015	160 = LaBarbera, 2016
41 = Sharma and Scott, 2015	101 = Cressey et al., 2015	161 = Macer, 2012
42 = Smith et al., 2013	102 = Cyranoski and Reardon, 2015a	162 = Cicerone et al., 2015
43 = Smith et al., 2012	103 = Fessenden, 2015	163 = Olson, 2016
44 = Bosley et al., 2015	104 = BioInsights, 2015	164 = Friedmann, 2016
45 = Murphy, 2012	105 = Keller, 2015	165 = IBC, 2015
46 = Malmqvist, 2011	106 = Kim, 2015	166 = NASEM, 2015
47 = Tonkens, 2015	107 = Kolata, 2015	167 = Alvis, 2016
48 = Heidari et al., 2017	108 = Larson and Schaffer, 2014	168 = Cicerone and Dzau, 2015
49 = Braun and Dabrock, 2016	109 = Ledford, 2015a	169 = Collins, 2015
50 = Mariscal and Petropanagos, 2016	110 = Lokody, 2014	170 = AMS, 2015
51 = Quilter, 2016	111 = Pollack, 2014	171 = ISSCR, 2015
52 = Witzany, 2016	112 = Reardon, 2015f	172 = SDB, 2015
53 = Henrich, 2011	113 = Reardon, 2015a	173 = Lentzos, 2015
54 = Charo, 2015	114 = Reardon, 2015e	174 = Thompson, 2015a
55 = Newson and Wrigley, 2015	115 = Regalado, 2015c	175 = Thompson, 2015b
56 = Werner-Felmayer and Shalev, 2015	116 = Regalado, 2015d	176 = Benjamin, 2015
57 = Araki and Ishii, 2016	117 = Regalado, 2015b	177 = Sarewitz, 2015
58 = Bourne et al., 2012	118 = Regalado, 2015a	178 = Comfort, 2015
59 = Elster, 2011	119 = Rojahn, 2014	179 = Terry, 2015
60 = Chan et al., 2015	120 = Stein, 2015	180 = Lundberg and Novak, 2015

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Supplemental data 1. Full search string

((Clustered Regularly Interspaced Short Palindromic Repeats [tiab] OR Caspase 9 [tiab] OR CRISPR-Cas Systems [MeSH] OR Zinc Fingers [tiab] OR Crispr-cas [tiab) AND (Germ Cells OR Blastocyst OR Fetal therapies OR Fetal stem cells OR Germ-Line Mutation OR Semen OR Reproductive medicine OR Reproductive techniques, assisted OR Gamete* [tiab] OR Sperm [tiab] OR Spermatid* [tiab] OR Spermato* [tiab] OR Ovum [tiab] OR Oocyt* [tiab] OR Oogoni* [tiab] OR Egg* [tiab] OR Embryonic stem cell* [tiab] OR ESC [tiab] OR Embryo* [tiab] OR Blastocyst* [tiab] OR Fetal* [tiab] OR Zygot* [tiab] OR Germ line [tiab] OR Germline [tiab] OR Germ-line [tiab]) AND (Therapy [MeSH] OR Therapeutics [MeSH] OR Gene targeting [MeSH] OR Cell engineering [MeSH] OR Genetic engineering OR Genetic therapy OR Targeted gene repair OR Engineer* [tiab] OR Develop* [tiab] OR Target* [tiab] OR Modif* [tiab] OR Induc* [tiab] OR Alter* [tiab] OR Interven* [tiab] OR Therap* [tiab] OR Target* [tiab] OR Edit* [tiab] OR advanced therap [tiab] OR advanced cell therap [tiab]))
OR
((Clustered Regularly Interspaced Short Palindromic Repeats [tiab] OR Caspase 9 [tiab] OR CRISPR-Cas Systems [MeSH] OR Zinc Fingers [tiab] OR Crispr-cas [tiab) AND (Germ Cells OR Pluripotent stem cells OR Embryo research OR Blastocyst OR Fetus OR Fetal therapies OR Fetal research OR Fetal stem cells OR Germ-Line Mutation OR Semen OR Reproductive medicine OR Reproductive techniques, assisted OR Gamete* [tiab] OR Sperm [tiab] OR Spermatid* [tiab] OR Spermato* [tiab] OR Ovum [tiab] OR Oocyt* [tiab] OR Oogoni* [tiab] OR Egg* [tiab] OR Embryonic stem cell* [tiab] OR ESC [tiab] OR Embryo* [tiab] OR Blastocyst* [tiab] OR Fetus [tiab] OR Fetal* [tiab] OR Zygot* [tiab] OR Assisted reproduct* [tiab] OR ART [tiab] OR Reproductive medic* [tiab] OR Germ line [tiab] OR Germline [tiab] OR Germ-line [tiab] OR pluripotent stem cell* [tiab] OR Germ cell* [tiab] OR semen [tiab] OR reproductive tech* [tiab]) AND (Ethics OR Eugenics OR Morals OR Social Values OR Social Norms OR Role OR Virtues OR Social Change OR Humanism OR consensus OR discussion OR Implicat* [tiab] OR Challenge* [tiab] OR Socio* [tiab] OR Ethic* [tiab] OR Informed consent [tiab] OR Bioethic* [tiab] OR Responsib* [tiab] OR Eugenic* [tiab] OR Legislat* [tiab] OR Jurisprud* [tiab] OR Risk* [tiab] OR Advers* [tiab] OR Moral* [tiab] OR Virtue* [tiab] OR Personhood [tiab] OR Principle* [tiab] OR Humanis* [tiab] OR consensus [tiab] OR discussion [tiab]))
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sion [tiab]) AND (germline modification [tiab] OR germline editing [tiab] or germline gene editing [tiab] OR germline alteration [tiab] OR germline intervention [tiab] OR germ-line modification [tiab] OR germ-line editing [tiab] OR germ-line gene editing [tiab] OR germ-line alteration [tiab] OR germ-line intervention [tiab] OR germ line modification [tiab] OR germ line editing [tiab] OR germ line gene editing [tiab] OR germ line alteration [tiab] OR germ line intervention [tiab]))
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OR
(((Genetic therapy/Ethics) OR (Genetic therapy/legislation & jurisprudence)) AND (Germ Cells OR Blastocyst OR Fetus OR Fetal therapies OR Fetal stem cells OR Germ-Line Mutation OR Semen OR Reproductive medicine OR Reproductive techniques, assisted OR Gamete* [tiab] OR Sperm [tiab] OR Spermatid* [tiab] OR Spermato* [tiab] OR Ovum [tiab] OR Oocyt* [tiab] OR Oogoni* [tiab] OR Egg* [tiab] OR Embryonic stem cell* [tiab] OR ESC [tiab] OR Embryo* [tiab] OR Blastocyst* [tiab] OR Fetal* [tiab] OR Zygot* [tiab] OR Germ line [tiab] OR Germline [tiab] OR Germ-line [tiab])) OR (((Genetic therapy/therapy) OR (Genetic therapy/therapeutics)) AND (Ethics OR Bioethics OR Social Responsibility OR Eugenics))

Supplemental table. Reporting of domains over time

Domain	Reporting on domains per year					
	2011		2012		2013	
	N	Reference	N	Reference	N	Reference
Quality of life of affected individuals	9	1-9	5	10-14	9	15-23
Safety	9	1-9	4	10,11,13,14	7	15-19,21,23
Effectiveness	4	1,5,7,9	2	11,14	5	16,17,19,21,23
Existence of a clinical need or alternative	4	5-7,9	2	10,14	2	17,23
Costs	0		1	14	1	19
Homo sapiens as a species	7	2-7,9	3	10,13,14	7	15-17,19,21-23
Social justice	5	2,5-7,9	3	11,13,14	4	17,19,20,22
Potential for misuse	3	1,3,5	1	14	2	15,17
Special interests	0		1	10	0	
Parental rights and duties	7	2,3,5-9	3	10,11,14	3	20,22,23
Comparability to acceptable processes	9	1-9	4	10,11,13,14	5	15-17,20,22
Rights of the unborn child	5	2,4,6-8	3	11,13,14	2	17,20
Human life and dignity	7	1,2,4,6-9	4	10,12-14	3	17,20,23
TOTAL	9	1-9	5	10-14	9	15-23

*Articles were included until June of 2016
Reference numbers correspond to references in Table IV.

2014		2015		2016*		p-value for difference between 2011-2014 and 2015-2016
N	Reference	N	Reference	N	Reference	
9	24-32	116	33-148	27	149-175	0.59
9	24-32	111	33-37,39-118,120-123,125-143,176-178	25	149-159,162-174,179	0.73
7	24-26,28-30,32	94	33,34,37-48,50,52-70,72,73,75-87,89-97,99-101,103,105-113,115-118,120-123,126,129-131,133,135,136,138-141,144,145,147,177	20	150-152,154,155,157-160,163-170,172-174	**0.03**
4	24-26,29	48	34,36,41,43-45,47,50,52,53,55,56,58-63,65-67,69,70,77,79,83,86-89,94,95,97,101-103,110,112,113,117,121,123,127,132,133,135,138,142	15	149,151,154,157,159,163-170,172,173	0.69
3	24,26,29	38	33,43,45,46,50,52,53,56,57,59,61,65,66,70,72,76,79,88-90,93,94,96,97,100,106,110,112,113,115,118,120,123,125,139-141,145	8	157-159,161,166-168,173	0.09
3	24,28,30	80	33,34,38-44,46-58,60-67,69,71,73,75-77,79,80,83-85,87-90,92-94,96-103,105,108,109,112,113,117-120,123,125-127,129,131,133-135,138,140,141,143,147,148	14	149,151,153,157-159,162,165-167,170-173	1.00
1	24	31	43,44,47,50,52,53,57,61,66,67,69,72,79,80,83,89,94-99,102,105,108,125,129,132,136,141,148	10	151,152,157-159,165,166,171-173	0.20
1	24	35	33,38,43,47,50,51,57,58,61,63,65,66,68,70,76,79,81,84,89,93-95,97,100,104,113,120,123,125,134,136,137,139,140,144	12	150,151,154,157-159,161,162,165,171,173,179	**0.30**
3	26,29,32	41	40,43,45-48,51-57,61,69,72,78,85,89,91,93,94,96-99,104-106,109,113,117,119,120,123,127,137,140,143,144,148	7	151,157-159,162,168,169	**0.03**
2	24,31	20	44,49,50,52,58,59,61,63,68,69,79,88,89,95,96,105,125,129,139,140	10	149,157,166-173	**0.003**
1	26	33	40,45,46,49,50,52,54-57,59-61,63,66,67,79,87-89,93-95,97,101,105,123,128,129,131,134,139,176	11	149,157,158,162,165,166,168,170-173	0.002
2	24,31	26	43,44,49,52,59,61-64,66,69,72,78,89,93,94,96-99,113,121,123,129,135,139	9	151-154,157,166,168,170,179	0.12
3	24,28,31	33	45-47,49-54,56-59,61,63,64,66,68,69,77,85,89,94,97,99,105,123,132,134,137,141,145,148	11	149,151,154,155,157,159,166,170-173	0.01
9	24-32	120	33-148,176-178,180	28	149-175,179	N/A

"The question of humanness and thus what constitutes a human being is an anthropological question that people have dealt with for centuries"

-European Commission report, 2021. Ethics of genome editing

CHAPTER 7

Dynamics of reproductive genetic technologies: perspectives of professional stakeholders

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Accepted for publication.

Abstract

Reproductive and genetic medicine are evolving rapidly, and new technologies are already impacting current practices. This includes technologies that can identify a couples' risk of having a child with a genetic disorder. Responsible implementation of new technologies requires evaluation of safety and ethics. Valuable insights for shaping governance processes are provided by various stakeholders involved, including healthcare professionals. Their willingness to adopt these technologies and guide the necessary systemic changes is required for the successful implementation of these technologies. In this study, twenty-one semi-structured interviews were conducted with professionals from different disciplines in the field of reproductive and genetic healthcare in the Netherlands. Three emerging technologies were discussed: expanded carrier screening (ECS), non-invasive prenatal diagnosis (NIPD) and germline genome editing (GGE). By probing stakeholders' views, we explored how culture, structure and practice in healthcare is being shaped by innovations and changing dynamics in genetic and reproductive medicine. The general consensus was that the implementation of reproductive genetic technologies nationwide is a slow process in Dutch healthcare. Stakeholders referred to a "typical Dutch approach" that is characterized by restrictive legislation, broad support for people living with disabilities, values of an egalitarian society and limited commercialisation. Different scenarios for embedding ECS in future practice were envisioned, while implementation of NIPD in clinical practice was considered obvious. Views on GGE varied among stakeholders. Previous implementation examples in the Netherlands suggest introduction of new technology involves an organized collective learning process, with pilot studies and stepwise implementation. In addition, introducing and scaling up new technologies is complex due to delay from the legislative framework and the complex relationship between the government and stakeholders in this area. This paper describes how the international trends and advances of technologies are expected to manifest itself in a national setting.

Expanded carrier screening (ECS) determines the carrier status of an individual / couple for multiple recessive disorders simultaneously, and aims to identify couples at increased risk for having affected offspring in order to inform reproductive decision-making. ECS is ideally performed before pregnancy. Couples from the general population can opt for ECS, regardless of their risk based on ancestry.

Germline Genome Editing (GGE) involves modification of the DNA of early embryos, sperm or oocytes, potentially preventing genetic disorders. Genetic changes can be passed down to future generations. Currently, GGE is not allowed and it is not expected to be available in the near future.

Non-Invasive Prenatal Diagnosis (NIPD) screens for specific autosomal recessive or dominant disorders by analysing fetal cell free DNA (cfDNA) isolated from maternal plasma. Pregnant women with an increased risk of having an affected child in the absence or presence of a positive family history or after ultrasound with abnormal results suggesting dominant disorders are eligible. NIPD can be a non-invasive alternative for PND (see below). It is expected that NIPD will be available for a growing number of disorders.

Non-Invasive Prenatal Testing (NIPT) allows for the screening of fetal aneuploidies (including trisomy 13,18 and 21) by analysing cfDNA isolated from maternal plasma of pregnant women. Detection of aneuploidy allows women to prepare for the birth of an affected child or to terminate the pregnancy. NIPT is available in many countries.

Prenatal Diagnosis (PND) refers to invasive procedures like chorionic villus sampling and amniocentesis that are preformed prenatally to detect specific genetic and/or chromosomal abnormalities in high risk pregnancies. The test result allows women to prepare for the birth of an affected child or to terminate the pregnancy. PND is available in many countries.

Preimplantation Genetic Testing (PGT) involves genetic analysis of a single cell or small number of cells of an early stage embryo for a specific known genetic or chromosomal disorder. The embryos are created through in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI). An unaffected embryo is transferred to the uterus. Confirmation of the PGT results by PND is offered because of a small residual risk of a PGT misdiagnosis. PGT is available in many countries for couples at increased risk.

Box 1. Definitions of technologies discussed in the interviews

Introduction

The development and introduction of new technologies in healthcare is constantly evolving, including reproductive and genetic medicine. Premature implementation of new technologies can be an actual risk in reproductive medicine for (future) recipients [1], and therefore thorough safety evaluation of technologies is needed [2]. Implementing new technologies in an existing field involves changes and transitions for a broad range of stakeholders in organizing (structure), thinking (culture) and doing (practice) [3]. All stakeholders involved should thus be engaged to ensure responsible implementation. Two leading professional organisations, the European Society of Human Genetics (ESHG) and European Society for Human Reproduction and Embryology (ESHRE), published a statement in 2018 on emerging topics at the interface of reproductive and genetic medicine [4]. Among these, several new technologies were listed (Box 1), including expanded carrier screening for assessing reproductive genetic risk, non-invasive prenatal testing and diagnosis, and germline genome editing. There are calls for regulation of these, and other, new reproductive genetic technologies [2, 4-6], supported by arguments that these impact not only end-users but future generations [7]. Technological advances surpassing capabilities of current clinical practices cause shifts in among others, information provision, uptake, availability, and costs. Therefore, it is relevant to study the interplay of these technologies in more detail to anticipate possible shifts in use, which are not straightforward due to various stages of development and/or implementation within the healthcare system, and consequential impacts on uptake.

Preconception carrier screening informs prospective parents if they are a carrier couple for a specific autosomal recessive or X-linked disorder and thus obtain information about their increased risk of having a child with that disorder before pregnancy. Traditionally, preconception carrier screening was offered for a limited number of disorders to certain high-risk groups based on ancestry. Next-generation genome sequencing has made it possible to expand the number of conditions screened, hence the term expanded carrier screening (ECS). Evolving sequencing technology also has lowered costs to the point that ECS can be, in principle, offered to all prospective parents [8]. One option for couples who have an increased risk for having an affected child is preimplantation genetic testing (PGT), in which unaffected embryos are selected prior to implantation in the womb. During pregnancy, another option is invasive prenatal diagnosis (PND), where the chorionic villus or amniotic fluid is sampled to test for a known familial disorder in the fetus. If more carrier couples are identified with ECS, the need for PGT, PND or non-invasive prenatal diagnosis (NIPD) could

increase [9]. NIPD, which is based on analysis of foetal cell-free DNA (cfDNA) from maternal blood, is a non-invasive method that will likely soon become widely available and for many conditions, opening the door to analysis of the entire foetal genome [10]. CfDNA sequencing also allows screening for specific foetal chromosomal aneuploidies in non-invasive prenatal testing (NIPT), a technology which is already broadly implemented internationally [11, 12]. Both NIPT and NIPD are expanding to include more disorders, as the sequencing costs continue to decrease. Another emerging technology that was discussed by the ESHG and ESHRE [4] is germline genome editing (GGE). With GGE, the DNA of embryos or germ cells could be modified to prevent genetic disease. Great commotion was caused across the globe when the first case (and last up to now) of genome edited babies in China was reported [13]. However, a global moratorium is in place that prohibits GGE in a clinical setting (i.e. transfer of embryo to the uterus) as current technological practices may be harmful to the embryo and raise serious ethical and fundamental concerns [14].

The successful implementation of new technologies is largely dependent on adoption by crucial stakeholders [15]. In order to guide responsible introduction of new technologies, governance is necessary. Assessing stakeholders' views is critical to obtain insight into the deployment process and assess necessary changes, moreover, to raise awareness among stakeholders and wider audiences. Table 1 presents an introduction to the key characteristics of the Dutch healthcare system, and an overview of the currently available reproductive genetic technologies, along with emerging technologies possibly available in the future.

The emerging technologies discussed in this study are expected to have a large impact on the field of reproductive medicine and genetics in the near future [4]. This makes exploration of Dutch stakeholders' perspectives and expectations concerning the future development and possible implementation of ECS, NIPD and GGE in the existing reproductive genetic healthcare field extremely relevant. We discuss how international trends and new technologies are expected to manifest in a national setting.

Table 1. The context of reproductive genetic technologies in the Netherlands, discussed in this study

Healthcare system in the Netherlands	Current application of reproductive genetic technologies	
The healthcare system in the Netherlands is controlled by the government together with private health insurance companies: a public-private system. The government has the responsibility of monitoring the quality of care and setting healthcare priorities. Everyone in the Netherlands is obliged to join a health insurance company for a basic package of care (expanded at will, at people's own expense) to access healthcare. The Health Insurance Act (Zorgverzekeringswet) is in place since 2006. In this basic healthcare package, a consultation with the general practitioner, prescription drugs or hospital visits, including a clinical geneticist consultation, are included [16]. It should be noted that every person of 18 years or older pays at least a yearly out-of-pocket amount of €385 before being reimbursed for healthcare. General practitioner visits are exempt.	**ECS***	Since 2020, a professional guideline for carrier screening in the Netherlands has been developed to indicate which tests are needed for which at-risk groups (i.e. ancestry-based, consanguinity) [17]. As of today, carrier screening is not broadly offered to the general population, i.e. people without an increased risk, and private commercial providers are forbidden to offer this due to legislation [18]. Since 2016, two (out of the country's eight) University hospitals [19, 20] offer an ECS panel of 50-70 conditions available to the general population. At the time of this study, these tests are not reimbursed by national healthcare, and costs range between €650-€1100.
	GGE	GGE is currently illegal in the Netherlands, similar to many other countries. Research on human embryos is not allowed beyond 14 days and embryos cannot be created for research purposes. Initiated by the Ministry of Health Welfare and Sports and other organisations, 'The Dutch DNA-dialogue project' about GGE took place in 2019-2020. The dialogue was organised among different stakeholder groups including the general public, prospective parents, and children at primary and high school level in order to collect a broad range of views from the Dutch general public on GGE and invite stakeholders to form opinions on the matter [21].

Table 1. The context of reproductive genetic technologies in the Netherlands, discussed in this study *Continued*

Healthcare system in the Netherlands	**Current application of reproductive genetic technologies**	
	NIPD	At the time of this study, NIPD for the detection of monogenic disorders is not yet available in the Netherlands. A pilot study to evaluate the diagnostic accuracy of NIPD for monogenic disorders around 8-10 weeks of gestation is ongoing, but suffers from low participation and was temporarily halted due to the COVID-19 pandemic. It is expected that NIPD will eventually be available to couples with a known increased risk on having an affected child.
	NIPT	Implementation of NIPT for all pregnant women in the national prenatal screening program has been executed in a study (TRIDENT-2 [22]). Professionals have organized a Dutch NIPT Consortium that works closely with the government [11]. This allows for thorough evaluation of the implementation process, including ongoing research into the cultural acceptability of NIPT, and the counselling and training of healthcare professionals. At the time of this study, the NIPT is available to all women as a first trimester screening test (cost €175).
	PGT	PGT has been available in the Netherlands for over 25 years. An independent committee is reviewing the eligibility of new indications. There are four academic hospitals that offer counselling for PGT treatment. Only one centre (Maastricht UMC) has a government permit to perform the actual diagnostic DNA testing on the embryos. Three cycles of in vitro fertilization along with intracytoplasmic sperm injection are reimbursed.
	PND	To identify a (specific) chromosomal abnormality, a familial pathogenic DNA variant, or a genetic syndrome, invasive prenatal diagnostic testing (chorionic villus sampling or amniocentesis) is offered to high-risk couples and reimbursed.

Abbreviations: ECS=expanded carrier screening, GGE=germline genome editing, NIPT=non-invasive prenatal testing, NIPD=non-invasive prenatal diagnosis, PGT= preimplantation genetic testing and PND= prenatal diagnosis.

Materials and Methods

Study design: A qualitative study design using semi-structured interviews was applied for this study. The Medical Ethical Committee of the Amsterdam University Medical Center (location AMC) approved the study protocol and exempted this study from ethical review (W18_054).
Theoretical Framework: Two theoretical models, the Constellation Perspective and the Network of Actors model, were used for the study design and the interpretation of findings. The Constellation Perspective [23] argues that a (healthcare) system can be seen as a constellation of interrelated practices and relevant structuring elements, and can be described by its (i) structure (organizational and power structures), (ii) culture (values and thinking) and (iii) practice (actions and implementation) (Figure 1). According to this model, actors (stakeholders) determine structure and culture. Actors are known to generally be hesitant to change, for example to adopt a new technology that is (not yet) concordant with the structure or culture of the existing system. When new technologies are developed and implemented in an existing (healthcare) system, transition occurs when fundamental changes in all three aspects of the system happens. Key actors in the field can either hinder or facilitate change, and act as change agents [3, 24].

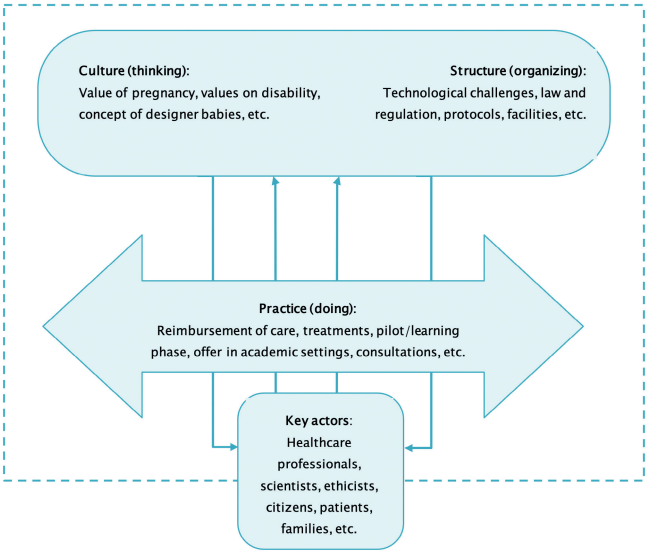

Figure 1. The existing system of reproductive medicine: operationalization of the constellation concept into structure, culture and practice, adapted from Rigter [25] and van Raak [23].

The Network of Actors model can be used to identify and describe the key actors involved in the process of development and implementation of new technologies [26]. Moreover, this model is helpful to gain in depth understanding of the roles of stakeholders and their interaction. According to this model, the different actors are divided in four categories: (i) the scientists who develop and do research into the *technology*, (ii) policymakers and ethicists who decide whether a technology is *acceptable* and should be made available, (iii) the healthcare providers who *organise* implementation of a technology in the actual healthcare system and offer it to recipients, and, last but not least, (iv) the citizens and patients who may use or *demand* a technology (Figure 2). The existing model does not include the industry; however, we believe this stakeholder group is almost indispensable when discussing new technologies, both for development and implementation in health care. Dynamics occur if a certain technology is being developed, an organization is ready to implement the new technology or approaches, if there is a demand among (prospective) users for new practices, and if developments are considered acceptable. This model facilitates exploring expectations and actions of the various stakeholders when attuning the use of technologies in a changing field. It should be noted that, in practice, stakeholders may have different roles to fulfil at the same time, e.g. working as a healthcare provider and policy adviser to the government. The sources of dynamics and roles/ categories of actors involved are interrelated and merged in Figure 2 [3, 26].

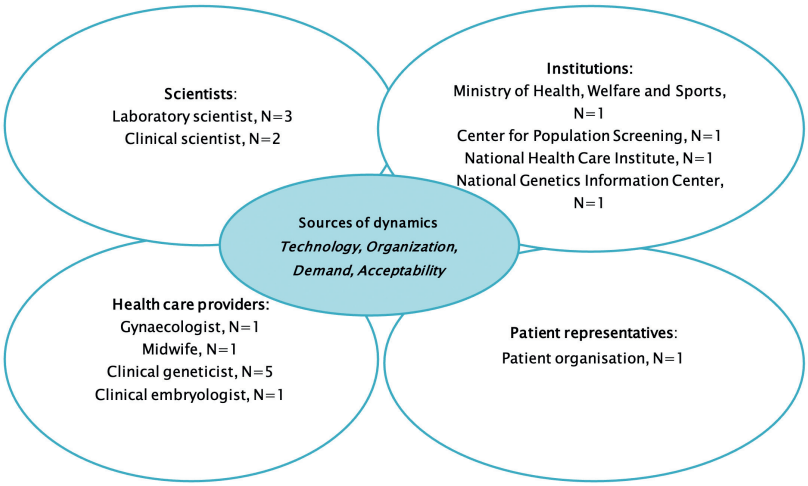

Figure 2. Network of Actors model, adapted from Achterbergh et al. [26]. The numbers of interviewees per stakeholder group are indicated with N= x.

Participants and procedure: A total number of 28 key stakeholders were identified with purposive sampling and 21 stakeholders were interviewed. Representing healthcare professionals including gynaecologists n=1, midwives n=1, clinical geneticists n=5 and clinical embryologists n=1, researchers including, laboratory n=3 and clinical n=2 scientists, professionals from industry n=1, institutions including, governmental n=2 and health insurance institutions n=1, ethicists n=2, legal experts n=1, and representatives from patient organisations n=1 (Figure 2). It should be noted that participants had different expertise and knowledge concerning the discussed technologies (i.e. some participants work solely in the field of PGT). The perspectives of couples who face an increased risk of having affected offspring, representing the stakeholders that may voice "demand" for these techniques, have been published elsewhere [27]. Relevant stakeholders were contacted through email with an invitation letter, four stakeholders replied that they did not consider themselves suitable for participation in this interview study, and three stakeholders, working for institutions and in healthcare, did not reply. From December 2019 until February 2021, twenty-one interviews of approximately 45 minutes were conducted (n=5 face-to face and n=16 online due to the COVID-19 pandemic) by one researcher (I.D.) who is trained in conducting interviews. All respondents were based in the Netherlands and/or affiliated with Dutch institutions.

Interview guide: The following topics were discussed in the interviews: (i) Stakeholders' own role, their current activities, their responsibilities and observed demand for these developments, (ii) expectations regarding the impact of the technologies on the existing field and current practice, and (iii) expectations regarding the dynamics between current and future technologies (i.e. ECS, NIPD/NIPT, PND, PGT, GGE).

Data analysis: All interviews were recorded after participants' agreement and transcribed verbatim. For collecting and analysing qualitative data, we adhered to the COREQ checklist [28]. The qualitative data software Atlas.ti 8 was used for analysis. First, open coding was performed and the perceived relevant items of the data were marked in the transcripts. Second, thematic content analysis was conducted. To increase validity, five transcripts were coded by two researchers independently [C.E. and I.D.]. The codes were compared, discussed and adapted until agreement was reached. All other transcripts were coded by one researcher [I.D.]. Themes and topics were selected for several reasons: most expressive, repeatedly identified, or remarkable cases. The quotes that were considered most relevant for illustration of the results were translated into English. The stakeholder group and the interview number (participant; P1, 2, 3...) are indicated with the quotes.

Results

The results of this study are structured into two identified themes. The first theme, "The typical Dutch approach", illustrates the views on the current (reproductive genetic) healthcare system in the Netherlands by describing experiences of stakeholders with earlier implementation of genetic technologies in terms of current practice, and important structural and cultural elements. The second theme, "Moving forward with new technologies", discusses the expectations concerning ECS, NIPD and GGE and their potential impact in detail.

Theme 1: The typical Dutch approach

Participants framed the dynamics of new technologies within a cultural background. The typical Dutch approach emerged as a theme from discussing previous examples and experiences and looking forward on the new technologies. It was mentioned that the Netherlands acts carefully, but as a consequence is not a pioneer in reproductive technology worldwide. They argued that technologies tend to be implemented only under certain conditions imposed by the government. Legislation, such as the Dutch Population Screening Act, contributes to accurate implementation of screening and aims to protect people against potential harm [29]. Several respondents called this a "conservative approach" when it comes to research and implementation of new (reproductive) technologies:

> *"We have a government that handles the changes it wishes to pursue very responsibly. In the Netherlands, change is never immediate and even the smallest decisions get weighed and measured for pros and cons. (...) Look, we don't usually lead the way: we like rules, laws and discussion too much for that, but we are never really behind the curve. But we're not forerunners."* P9, institution.

This sometimes frustrates stakeholders as they believe that certain legislation is too strict, hindering research and innovation and risking progress within the country:

> *"I don't understand why some processes here are so slow, it frustrates me. I contact a colleague abroad and hear that some techniques or tests are already being offered on a structural basis. We [referring to the Dutch government] are sometimes too strict."* P4, healthcare provider.

In terms of actors influencing the reproductive healthcare system, some interviewees believed that professionals working in the field have an important role in the organization and implementation of new technologies, with the support of government policy. Stakeholders explain professional groups and consortia working in the field see it as their responsibility to develop guidelines based on state-of-the-art knowledge, in order to ensure people receive the best available care.

Participants believed that the political landscape has some influence as well. After elections the Dutch government changes every four years and, according to some participants, this heavily influences the healthcare system. For example, if more conservative parties are elected, the availability or progress of implementing certain reproductive technologies may be affected. One respondent argued that once benefits of a certain technology are proven, it should be available to people, regardless of the political nature of the government:

"It seems to me that a government which is unable to call upon Christian or other conservative beliefs would have a hard time stopping such change(s). So, I assume that all these developments, when safe and effective, would in some way manage to find a spot in the healthcare system." P13, healthcare provider

Some stakeholders were somewhat hesitant describing their own role in the implementation of new technologies. However, all believed that participating in research was an important societal responsibility when working in the field of reproductive and genetic care.

Cultural background

Implementation of a new genetic technologies are greatly influenced by the cultural background, as was mentioned by participants. Several norms and values were mentioned that are characteristic of Dutch culture: (i) An egalitarian society, (ii) Concerns of medicalisation of pregnancy and autonomous decisions, and (iii) Support for people living with disabilities.

(i) The importance of an egalitarian society. It was considered important by stakeholders to maintain healthcare services that are accessible for all. Some described this as an "Egalitarian society":

> *"In the Netherlands, we have a pretty egalitarian society, causing people to quickly call out: 'Hey, but this shouldn't just be for the happy few?"* P14, institution.

For example, the Netherlands was one of the first countries to integrate NIPT into routine prenatal care, making it widely available for all pregnant women,

albeit with a fee that may deter a proportion of women (Table 1). Another example was the three IVF/ICSI cycles within the PGT process that are reimbursed for most couples who face no contraindications. A member from an institution mentioned that this egalitarian approach sometimes creates difficulties for the government, for example, in a possible scenario where ECS is offered to everyone and fully reimbursed by the government:

> *"On what grounds do you decide that a technique should be collectively offered?"* P12, institution.

(ii) Concerns of medicalisation of pregnancy and autonomous decisions. Concerns about (over)medicalization, this involves situations where more medical care is applied to a health condition than is required or recommended to achieve better health. Earlier discussions about the medicalisation of pregnancy have been central to, for example, a cautious implementation of prenatal screening in the Netherlands. Some stakeholders argued couples have 'the right not to know' and should be able to opt out of screening. An important related concept in reproductive decision making is autonomy. Stakeholders agreed that everyone should be able to make their own autonomous decisions, and in the Netherlands, this includes declining tests or information about tests. Current policy and counselling guideline in the Netherlands are organized to support autonomous decision making. For instance, in prenatal screening, women are asked if they want to receive information about screening rather than being offered the screening directly. Moreover, feelings of any pressure to opt for certain technologies should be avoided, a member of an institution stated:

> *"I do think that it is very important that people receive proper support in this selection process [of opting for a specific technology] and that they do not experience any pressure. It is important to pay attention to the benefits as well as the potential harms."* P16, institution.

(iii) Support for people living with disabilities. The support for people living with disabilities is well established in the Dutch culture and healthcare. Some stakeholders thought this support could be threatened by the implementation of new technologies. When one can avoid having an affected child, treatments would still need to remain accessible.

> *"I really believe in prevention. But if people do not want that, the facilities should remain available to take care of people with certain conditions.*

> *We have to ensure the continued existence of services."* P4, healthcare provider.

Noticeably, respect for people with disabilities was often mentioned as another reason why the Dutch government is hesitant and careful in implementing preventative technologies like preconception carrier screening for the general public. In contrast, some others thought the attitude towards disabilities is sometimes 'romanticized' by favourable portrayal in the media, and this may lead to the general public underestimating the seriousness of some conditions.

Theme 2: Moving forward with new technologies

The expectations of stakeholders concerning ECS, NIPD and GGE are structured according to the three elements of the Constellation Perspective model; practice, structure and culture. In general, stakeholders mentioned that attention should be paid to the costs of emerging technologies. In the preconception context, stakeholders pointed to the lack of genetic literacy in the general public and the need to reach and inform couples that are not pregnant yet about for example the availability of ECS. The growing number of available reproductive technologies was said to possibly hinder autonomous decision making, highlighting the need to provide counselling to support the process.

Expectations of expanded carrier screening (ECS)

Practice: several possible future scenarios

The professional stakeholders interviewed outlined several possible scenarios for implementing ECS for the general population. Some mentioned that ECS can be embedded within fertility clinics, where prospective parents could be informed about the availability of the ECS test:

> *"I think it [ECS] should rather be integrated in reproductive medicine than in general healthcare, since prospective parents visiting fertility clinics have a clear child wish."* P19, institution.

Another suggested scenario was to incorporate ECS in general practice. It could be offered actively by a general practitioner, by inviting all patients of reproductive age to participate, or passively through a website or flyers.

Structure: expected changes

Several respondents believed that ECS will become an important new technology in reproductive medicine in the upcoming years. In terms of structure, some

stakeholders thought that ECS should be integrated with other aspects of preconception care, like lifestyle advice and assessment of medical risk factors:

> "ECS needs to be as established - just like taking folic acid when planning a pregnancy." P18, healthcare provider.

Stakeholders warned that the current capacity of PND and PGT would not be sufficient if ECS becomes mainstream. A stakeholder suggested that the role of geneticists could be expanded to provide training and support to other healthcare providers, in addition to counselling patients, which would require cultural and structural changes in the workplace. If ECS is implemented nationally, the costs of the test were frequently mentioned as a potential barrier, as not all couples may be able to afford it if not reimbursed:

> *"A shift towards preconceptional care will majorly depend on the accompanying costs of such a change. I think we should realise that as long as ECS is not covered by insurance, and people would have to pay for it themselves, then only a select group of our society can use it."*
> P5, scientist.

According to the stakeholders, ideally ECS should be fully reimbursed, however, this would be a major expense for the healthcare budget of the government. In addition to the expanded testing, healthcare providers will need additional education to provide counselling for ECS, one participant said. It was also noted that the test itself will likely become cheaper over time and therefore more accessible.

Culture: needs for cultural changes
Culturally, preconception care, or visiting a healthcare professional when planning a pregnancy, is not yet embedded in Dutch society, stakeholders mentioned. It was suggested, this could be related to the generally negative attitude towards medicalisation of pregnancy. It was stressed that genetic literacy is poor, and that society needs better education on autosomal recessive conditions. This will be challenging, stakeholders warned, given that most people are unaware of their risk:

> *"If it's not something that you see often in your personal surroundings, then people will not care about it. Everything keeps getting more medical, so people will keep wanting to know and be reassured more. If you look at*

it like that, more and more people would want to do this, but in truth this is not yet our experience." P4, healthcare provider.

According to some stakeholders, commercial companies that offer direct-to-consumer genetic tests play a crucial role in the growing public awareness concerning DNA and genetics. Some stakeholders expected that genetics, including carrier screening, will become 'normalized' to some degree. Subsequently, this will also have an impact on reproductive medicine and reproduction in general, they said. Meanwhile, interviewed members of institutions were hesitant about embedding ECS in national healthcare as a screening program. Reproductive screening can be a sensitive topic, and the government does not want to come across as pushing or 'sending a message' (i.e. support for people living with disabilities could be threatened) that screening should be seen as routine. Similar concerns were expressed earlier among members of institutions in the case of NIPT, as well.

Expectations of Non-invasive prenatal diagnosis (NIPD)

Practice: just a matter of time

At the time of this study, NIPD for monogenic disorders was not yet implemented in Dutch national healthcare (Table 1). Overall, professional stakeholders believed that it is just a matter of time before NIPD will be available in the Netherlands. Some stakeholders were actually surprised that NIPD is not yet available, because it is common for some genetic disorders in other countries such as the United Kingdom. One element is that the NIPD pilot study has made slow progress (partly due to the COVID-pandemic), according to one respondent. Furthermore, the broadening scope of NIPT, which is already implemented in healthcare, may blend diagnostics with screening with a combined NIPT/NIPD in the near future:

"Then there's of course the NIPD for monogenic disorders, which will be there in the coming years. We would initially use this for people who already have an affected child or who are affected themselves, so those with a higher risk. But if you then extend that, then you'll say: yes, well, if I have an NIPT for chromosomal anomalies, why would I not just add a little something for monogenic diseases?" P9, Institution.

A few stakeholders discussed their expectations concerning the use of whole exome sequencing (WES). With this technology, the coding regions (the exons) of all known (disease) genes of a person can be examined at once. Some stake-

holders anticipate that this technology will be offered to all pregnant women (via NIPT) in the future. This may facilitate the implementation of NIPD since foetal DNA will also be analysed.
Stakeholders suggested that NIPD could be a safer method to confirm the PGT test result (i.e. PGT pregnancies have a small residual risk of a misdiagnosis of 1 to 2%), given the minimal miscarriage risk with PND. Stakeholders did not believe that NIPD would become a more popular technology than PGT among couples, since PGT is preferred over pregnancy termination. Compared to the currently available prenatal diagnostic technologies, stakeholders listed only advantages of NIPD:

> *"The risk of a miscarriage after the results of the chorionic villus sampling or the amniocentesis, even if the chance is only 1 in 500, people still think it weighs very heavily, because it is their decision. If it is possible to do without this risk, with something just as reliable, quick and early in the pregnancy, then yes of course you'll choose that."* P15, healthcare provider.

Structure: a few challenges
A few drawbacks and technical challenges were anticipated for NIPD implementation. While stakeholders said that the technology is already very accurate, some challenges were mentioned, such as determining the inherited maternal allele of the fetus, assessing missing genetic information when there is a donor involved, and interpreting the results in case of only a small amount of cell free foetal DNA, in addition to communicating all the information to prospective parents. Moreover, the labour intensity of NIPD was mentioned as a drawback.

Culture: no expected need for cultural changes
The implementation of NIPD is not expected to require major changes in the way people think, so there is no need for cultural changes. PND is an accepted technology within society and NIPD would only broaden diagnostic opportunities for women with a known increased risk because the technology is non-invasive.

Expectations of germline genome editing (GGE)

Practice: far from clinical implementation
Many participants expressed that they expect that GGE is still far from clinical practice. Stakeholders had a wide range of thoughts and perspectives on the developments of GGE. Some believed that GGE will eventually be possible at some point, and will be used when proven safe for human use:

> *"If we know how to safely use GGE in humans, and I expect that we will in five or ten years, then it will happen. It already happened [...] If we are going to do this, it has to be in a safe way, and only on genomic diseases. But technologically speaking, it will definitely be possible."* P1, scientist.

Some stakeholders argued that it is a waste of energy and resources to invest in researching clinical application of GGE in reproductive medicine because there is an already established technology (i.e. PGT) that people will prefer because it is safer and more accepted:

> *"I think that people would always prefer the healthy embryo [referring to PGT] over 'let's correct the mutation' [GGE] and then restore the embryo."* P16, institution

Structure: several prerequisites

A stakeholder mentioned that in some countries the field of reproductive technologies is very much privatised and driven by profit rather than social responsibility. In terms of further development and to safeguard human use, stakeholders pointed to current laws and regulations (i.e. Dutch embryo law) that restricts research on human embryos beyond 14 days and bans the creation of human embryos for scientific purposes. It was argued that such laws hinder the development of technologies, like GGE in the reproductive context. Stakeholders had a common ground when it comes to regulation of GGE: good governance and regulation frameworks, nationally and internationally, should be in place to prevent abuse, to safeguard research and possibly guide human application. The costs of the technology were also mentioned: some believed it could be much cheaper than PGT while others believed this decrease in costs will take decades of research. Furthermore, there is a need to decide for what indications GGE would be reimbursed, but those decisions are very complicated, stakeholders said. This is especially difficult because GGE is still far away from clinical application and therefore it is impossible to draft reimbursement frameworks or costs-benefit analysis already. Stakeholders expressed that, in general, reimbursing treatments within reproductive medicine is complicated because the question arises whom you would insure, the future child or one of the parents: "It is actually about insuring a non-existing entity, namely an embryo." P17, institution.

Culture: a lot of hesitation

All stakeholders agreed that societal discussions of GGE are crucial, and require engaging all stakeholders involved in the decision-making process to guide further development and potential implementation. It was raised by stakeholders that the hype around GGE could create a technology push that we should guard against. Stakeholders who had a more positive attitude towards GGE suggested that society just needs time to get used to this heavily debated technology, and that people will eventually understand the benefits of it:

> *"GGE slippery slope? No, it's just further development. I mean choosing your car over your bicycle is also a slippery slope. What you see is that at a certain point technology becomes more and more normal in your daily life."* P7, industry professional.

Stakeholders who were hesitant to believe that GGE will actually become available for human use brought up several topics such as designer babies and creating 'superhumans'.

> *"I'm not a supporter of this, there are too many unanswered questions. And aside from that, we are moving towards the creation of the Übermensch and designer babies."* P15, healthcare provider.

GGE was often compared with PGT. Some stakeholders believed it could be a 'PGT+': for couples in which PGT is not successful, GGE could increase the success (pregnancy) rate. People who had moral objections to discarding embryos and therefore refrain from PGT could opt for GGE as a reasonable alternative. However, one respondent stated that selection will be part of a GGE procedure as well.

Stakeholders who were opposed to GGE believed its introduction would make it hard to draw a line between treatment and enhancement:

> *"I am an advocate for retaining the (distinct) medical line between enhancement and healing. If you cross that line, then I do not think that the added value of the germline editing is big enough for me to say: oh yes, let's lift/abolish the ban! Because yes, I think that with PGT we can really do almost everything, with the exception of a few tragic cases."* P20, scientist.

Discussion

By elucidating and clarifying the perspectives and expectations among Dutch professional stakeholders involved in reproductive and genetic care, this study contributes to an increased understanding of the prerequisites and challenges for responsible introduction of new (future) reproductive technologies (ECS, NIPD, GGE). From a constellation perspective, the expected and desired actions for responsible implementation of innovations in the reproductive healthcare field are described in terms of changes in practice, structure and culture [23].

Expected implementation of ECS, NIPD and GGE

Stakeholders envisioned different scenarios for the implementation of the three reproductive technologies reviewed here. For ECS, several structural changes may be necessary in order to become established in preconception care. More professionals will have to be trained to provide counselling, and reimbursement of the test will be needed to safeguard equal access, among others. Concerning NIPD, some stakeholders were surprised that this technology is not yet embedded in care as in other countries and all expected it will be as a matter of due course. In the prenatal context, few structural hurdles were identified for NIPD implementation, and availability for couples with a known increased risk seemed feasible on the short term. Expectations and views on GGE varied widely among stakeholders, but all believed that this technology is still far from clinical implementation. For GGE, structural changes were needed in the legal context to shape good governance.

The Dutch approach: slow but steady?

The results of this study show that the Dutch cultural background heavily influences the course of new technology implementation. The "Dutch approach" can be characterized by several aspects such as the value of inclusive dialogues and the importance of a learning phase. Although it is sometimes perceived as unnecessarily viscous, this Dutch approach also has advantages such as building public support and opportunities to learn from small-scale implementation. The insights gained from this method can also inspire and educate other countries.

Recently, the World Health Organization published recommendations for governance and oversight of human genome editing [30] and one of their recommendations was to facilitate an inclusive global dialogue. The ethical committees of the WHO and the European Commission furthermore recommended establishing a GGE-registry platform, where GGE research knowledge can be shared and used to help create oversight. As Turocy et al [31] suggested,

in their review on the progress and considerations of GGE, the way in which mitochondrial replacement therapy was handled in the United Kingdom could serve as a model. In implementing that technology, regulatory and ethical discussions involving stakeholders proved crucial for public acceptance of this therapy. Such a national dialogue on GGE has taken place in the Netherlands in 2019-2020, funded by the government [21]. Soliciting societal input and reaching consensus through public dialogue fits readily within the careful and reasoned Dutch approach. Indeed, the traditional "polder model" was founded on the involvement of all stakeholders to make decisions how to safeguard reclaimed land against flooding [32]. This method of consensus decision-making and co-operation despite differences continues to serve as an example for policy making internationally. Because GGE affects subsequent generations, GGE would benefit from a strong governance model with international oversight and cooperation. "Poldering", the slow decision-making process where all parties need to be heard, could be perceived justified or, alternatively, as a waste of time or harmful, e.g. when consensus is unfeasible or it unnecessarily delays safe implementation. Introduction of new technologies in an existing system could benefit from a learning phase, as brought forward by professionals in this study and previously described by van Schendel et al. for NIPT implementation [33]. Especially in the reproductive context, a careful implementation of potentially risky technologies that includes a pilot study and a learning period with suitable follow-up is important to determine adverse effects and establish safety. Unfortunately, history shows that some technologies were implemented prematurely, such as preimplantation genetic screening, this technology screens IVF derived embryos for aneuploidies. The increase in IVF success rate was added as an indication but this technology was introduced before thorough effectiveness studies, as previously argued [1]. A collective learning phase is considered valuable because participants can gain experience and anticipate structural changes. From the field of transition management and innovation science, we know that emerging innovations often first take place in a 'niche'. Those niche developments are described by Rotmans et al. as involving individual actors or technologies that can change the current practice of the social-technological landscape [34]. Successful niche developments need scaling up to gradually expand. The two currently available ECS initiatives in the Netherlands can serve as examples of a learning phase and evaluation might provide key insights to consider for potentially scaling up implementation [35, 36]. It was expected that the use of ECS will increase in the future by professionals in this study, although currently carrier screening is not widely available and public awareness is low [37]. Lessons learned from global initiatives could be shared, such as 'Mackenzie's mission'

in Australia [38]. The Australian federal government funds this pilot study that aims to screen 10,000 couples for 1,200 severe, childhood-onset genetic conditions in a research setting for three years.

International context: Structural and cultural differences, variable offers

Technologies are embedded in local practice, and are shaped by a national context where culture and structure define the reproductive healthcare system [23]. The core values of the "Dutch approach" shape the implementation of technologies, and this in particular distinguishes the Netherlands from many other countries where healthcare is often, to a larger extent, provided by commercial and private parties. Variability between countries was previously described in studies involving NIPT and ECS [11, 18]. An example is the high number of commercial providers in the United States that offer carrier screening [39]. Once high throughput sequencing was available at a reasonable price, commercial companies seized the opportunity to offer large screening panels to the general public [18]. The difference in healthcare systems could also be an explanation for the variability of ECS between countries [40, 41]. The Belgian reproductive healthcare system, for example, is differently organised compared to the Netherlands. Belgian women visit a gynaecologist on a regular basis, which simplifies opportunities for preconception counselling and increasing awareness of the availability of ECS. Since 2017, the Belgian Superior Health Council recommended to offer ECS for the general population and currently this is available from the clinical genetic centres for all couples at their own cost [42].

Important policy challenges

The main challenges of current policy seem to be the balance between accessible care for all, while keeping healthcare affordable. The careful consideration of evolving technologies and the egalitarian approach with a strong emphasis on equal access was mentioned in this study as important core values of the "Dutch approach". Previous evaluation studies of ECS in the Netherlands showed that a large number of participants considered the costs of the test too high and believed that it should be reimbursed by health insurance companies [43, 44]. The egalitarian approach favoured by the government is not achieved when out-of-pocket costs hamper equity in access. Whether reimbursement for all could be feasible was discussed by experts at a workshop held at the ESHG in 2015 on ECS [45]. Those experts agreed that equity of access was important, however, they also expressed doubts whether it was feasible because of the high cost of healthcare. The goal of an egalitarian society to avoid unequal access could delay implementation and scaling up innovative discoveries from niches.

Another challenge could be in defining the right actors for the implementation process, especially key stakeholders and/or so-called change-agents. Stakeholders often said it was the government's job to attune roles and responsibilities, and not many participants mentioned their own potential role in the process of responsible implementation. Conversely, the government also expects experts from the field to initiate and orchestrate these matters, which is a discrepancy that hides a potential structural problem.

Strengths and limitations

This qualitative research enabled rich and in-depth insights into the perspectives of various stakeholders involved in the field of genetic and reproductive health. Insights in what stakeholders view as prerequisites for responsible implementation of technologies in reproductive healthcare in a national context could also be relevant for developments in other countries. A broad range of professional stakeholders were included, which provided an extensive overview of expectations towards the technologies and the changing field. However, completeness of perspectives cannot be assured: general practitioners were approached several times per email but did not respond, and other perspective, e.g. the perspectives of health insurance companies, are missing, which we believe could have contributed valuable insights for the current discussion. All interviewed stakeholders are operating within the 'Dutch approach', perhaps a majority has the opinion the system they are supporting is doing things the right way. It would be informative to ask an expert perspective on the 'Dutch approach' from professionals in, for example, the United Kingdom, Iceland, or cultural more distinct country for example in Southeast Asia.

Conclusion

This study presents the perspectives of professional stakeholders from genetic and reproductive healthcare on three emerging technologies: ECS, NIPD and GGE. The general conclusion was that a careful and step-wise implementation of new technologies, referred to as the "Dutch approach", is desirable for achieving social acceptance and responsible use of innovative discoveries in line with existing practice, structure and culture. NIPD and ECS are expected to become widely available in the near future and in the case of NIPD with relatively few structural changes. The riskier technologies, like GGE, require a collective learning process, legal framework and inclusive dialogues on a national scale. Though the careful process of introducing new technologies can be perceived by some as an unnecessary waste of time, and one must be alert that useful

innovations are not unduly hindered by the complexity of the system. Continued attention should be paid to support sustainable processes for the responsible introduction of reproductive and genetic innovations.

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“Betekenis is te vinden waar praktisch nut en persoonlijk gewin meewarig het hoofd afwenden”

- Montessoro mon amour, van Ilja Leonard Pfeijffer

CHAPTER 8

General discussion

The field of reproductive and genetic health care is evolving extremely rapidly. For couples with a known increased risk for having an affected child with a genetic disorder, prenatal diagnosis (PND) and preimplantation genetic testing (PGT) are available at this point in time. Current implementation of advances in reproductive genetic technologies including preconception expanded carrier screening (ECS) and non-invasive prenatal diagnosis (NIPD) have altered the landscape of healthcare for prospective parents. Possible future deployment of technologies, such as germline genome editing or modification (GGE) and somatic genome editing (SGE), as a possible future treatment after the birth of an affected child, could also have major impacts [1]. Currently, GGE in the reproductive context is prohibited worldwide and, in the Netherlands, scientific research involving embryos is subject to strict legislation.

In this thesis reproductive genetic technologies are defined as technologies which enable reproductive decision making and/or inform people about their genetic risk of having affected offspring. Just like other technological advances, reproductive genetic technologies increasingly converge as they develop. Originally unrelated techniques may mutually influence each other, for example, an increase in uptake in carrier screening might change the need for other technologies, such as PND or PGT. International and national professional organisations emphasize that research concerning the desirability, demand and needs of prospective recipients, along with the support and expectations of providers, is of utmost importance before the implementation of new technologies in routine care [2, 3]. Therefore, this thesis explored the dynamics of these evolving reproductive and genetic technologies by examining the perspectives of various stakeholders with the aim of attuning responsible implementation.

This thesis aimed to gain more insight into the views on current and potential reproductive genetic technologies of four stakeholder groups: the general population, couples who desire children, couples who have an increased risk of having offspring with a genetic condition, and experts working in the field. This research helped uncover underlying opinions, beliefs and values that provide critical information for shaping the process of responsible implementation of these new technologies. The general discussion of this thesis first reviews the main findings of this research, how the findings relate to existing literature, followed by a reflection on the study's methodologies, strengths and limitations. Finally, the implications and recommendations for practice and further research are provided.

General reflection on main research findings

Expanded carrier screening: perspectives, experiences and the future
Expanded carrier screening (ECS) involves analysing prospective parents' DNA to determine their risk of having offspring with a genetic disease. Originally targeted at only a few genetic conditions, this screening has recently expanded to include hundreds of genes. Worldwide, ECS is mostly offered by commercial providers and it is not part of routine healthcare [4]. It is expected that the offer and uptake of ECS will continue to expand [5] due to ongoing technological developments and decreasing costs [4]. In the Netherlands, ECS is not included in national healthcare nor in insurance plans and commercial providers are not allowed. However, since 2016, two academic medical centres have developed an ECS test covering 50-70 severe autosomal recessive disorders that is available to all prospective parents for a fee.

In ***chapter 3***, we examined the perspectives towards this non-commercial ECS test among the general public and relatives of patients with mucopolysaccharidosis type III (a severe metabolic disorder also named Sanfilippo syndrome, MPS III) using a focus group study design. Both MPS III relatives and the general public supported a universal offer of ECS. Despite these positive attitudes, which were in line with previous studies [6-11], several important barriers were identified: a lack of awareness among the target population about the test availability, a lack of genetic knowledge in general, confusion of ECS with prenatal screening tests, a lack of personal relevance of the test due to low perceived risk, and practical barriers such as the cost of the test. A potential negative impact on psychosocial wellbeing and religious beliefs were also mentioned. Literature also showed that awareness of ECS and perceived risk of being a carrier couple is generally low [8, 9, 12], and that perceived benefits [13] and prior knowledge of ECS is associated with increased intended and actual uptake of the test [14]. Misconceptions about ECS, such as confusing it with prenatal screening for Down syndrome, were also mentioned in existing literature [15].

Differences in the perception of disease severity between the general public and relatives of patients with MPS III were noted: members from the general public classified disorders more often as severe and suitable for inclusion in ECS panels. Members from the general public also tended to have a more negative view towards disorders than family members of patients with a (severe) genetic disorder. This discrepancy was also found by Boardman et al. [16], who explained the difference in perspective as embodied knowledge due to having the condition oneself or knowing someone close (e.g. a child) with the condition. The role of this type of "experiential" knowledge on perceptions towards disorders was also

noted in another study by Boardman et al. that assessed the views of adults with haemophilia and their family members towards genetic screening [17]. They showed this group's support for including haemophilia in population screening programmes was primarily for the purpose of preparing for the birth of an affected child, rather than pregnancy termination [17]. Haemophilia has become a largely treatable condition, so therefore the reasoning of including haemophilia in screening panels might differ from the reasons of our study participants of including MPS III [11, 18]. Moreover, concerns about the stigmatization of people with genetic disorders have been previously raised by professionals [19]. In our study, however, relatives of MPS III patients expressed no concerns about any form of stigmatization ***(chapter 3)***. It can be concluded that different views are present in society and the possibility of stigmatization should not be excluded.

Chapter 4 describes the experiences of ECS test participants in a Dutch hospital setting. The group included high-risk couples and couples from the general population. Couples were considered at high risk of having a child with a genetic condition based on family history, consanguinity, ancestry and/or geographical background. Overall, the participants were very satisfied with the ECS test; all respondents said they would opt for ECS again and over 80% would recommend the test to others. Half of the participants (49.6%) considered the costs of the test (€650) too high. This result was supported by several studies that have assessed willingness to pay for ECS among the general public and reported only 3% were willing to pay the current test price [8, 10]. Attention should be paid to the possibility that costs are negatively impacting accessibility of ECS in the Netherlands, since our results show that it is currently too expensive.

For decades, carrier screening was available only for some high-risk groups. Regarding concerns that offering ECS to the general population might cause unnecessary anxiety [20], our results showed very limited negative psychological impact from the ECS test. Other studies on ECS [7, 21] and on carrier screening for single diseases such as cystic fibrosis [22] also showed no long term negative psychological consequences of the test. Some of the carriers had higher levels of distress compared to non-carriers, although not clinically relevant. This could possibly be minimised by disclosing only couple-based test results, where couples are informed of a positive result only if both partners are carriers for the same disorder. Full disclosure of individual test results was, however, preferred by the participants in chapter 3. Anxiety levels before testing were higher for pregnant participants and their partners ($p=0.01$). This supports the argument that ECS should preferably be offered before pregnancy. This would not only reduce anxiety, but allow for more time for decision making and provide a wider range of reproductive options.

Enabling people to make an informed decision when it comes to reproductive choices is the ultimate goal of an autonomous society. It has been argued that the expansion of the number of conditions in carrier screening, in combination with the growing number of reproductive options, would complicate decision making [23]. Our results dispute this. We showed that a majority of participants (86%) made an informed decision to participate in ECS, which was likely supported by the extensive pre-test counselling that was offered to all participants. However, it should be noted that no carrier couples were identified in this study population and most participants were highly educated, therefore research into informed decision making in ECS needs further scrutiny.

Dutch professional stakeholders working in the field of genetic and reproductive medicine expect an increase in demand for ECS in the coming years ***(chapter 7)***, as a consequence of the public's growing awareness of genetic and reproductive technologies. This reasoning by professionals is in line with a previously published joint statement of several obstetric and genetic American professional organisations [5], and a study assessing the views of European geneticists that indicated that efforts should be taken to facilitate access to ECS [24]. Increasing ECS means that the demand for genetic counselling will also greatly increase, to provide information needed to ensure responsible decision making. It was suggested by professional stakeholders in this thesis that the screening offer and counselling could be done by non-genetic professionals, such as general practitioners or midwives, similar to a study by Holtkamp et al. [25]. Another option which could reduce the burden on genetic counsellors while allowing couples the opportunity to inform themselves at their own pace, is informing prospective parents about ECS through information websites and flyers [24]. Some professionals expected that ECS for the general population would (and should) become part of the national screening programme, as this would enhance all prospective couples' autonomous decision making. However, policy makers showed a more reserved attitude. This reserved response was labelled by other stakeholders as 'typical Dutch' and refers to the fact that the Dutch government has not exactly been a pioneer in implementation of new reproductive genetic technologies in the past. For example, the implementation of NIPT screening in the Netherlands took much more time compared to surrounding European countries, however it was considered very carefully done [26].

Professionals stressed that it is important that couples are free to opt for ECS, especially if ECS become routine in national healthcare. Other ethical concerns, such as the medicalisation of pregnancy, equity of access, stigmatization of people living with disabilities, and impact of such a test offer on carrier couples should continuously be considered. However, these concerns will not likely be

barriers to routine implementation, as studies such as this continue to build support for the acceptance and widespread implementation of new technologies which facilitate informed decision making.

The current challenges for routine implementation of ECS in the Netherlands seem partly attributable to practical aspects, such as who is responsible for running the tests (beyond the current local initiatives), who will organise and offer information provision and counselling, and who will pay for the test [12, 25]. However, also ethical discussions such as the question whether ECS responds to an urgent problem or population need or the possibility of stigmatization of people with disabilities [19] and the inclusion of types of disorders in ECS panels seem to slow down implementation.

Non-invasive prenatal diagnosis: just a matter of time

Recent advances in genomics have led to new diagnostic tests that provide critical information at a very early stage of a pregnancy. Non-invasive prenatal diagnosis (NIPD) tests for single-gene disorders by analysing fetal DNA isolated from maternal plasma. In ***chapter 2***, couples with a known increased risk of having a child with a specific genetic disorder expressed a positive attitude towards NIPD for monogenic disorders, and considered it safer and less burdensome compared to invasive techniques (PND), such as chorionic villus sampling and amniocentesis, which carry a slight miscarriage risk. In addition, for those couples who had preimplantation genetic testing (PGT), NIPD is a safer method to confirm the genetic status of the fetus [27]. It is expected that wide-spread implementation of NIPD will reduce the need for invasive diagnostics for couples with an increased genetic risk [28, 29]. However, considering the perspectives of couples, it is not expected that NIPD will replace PGT, as for some couples, pregnancy termination, in case the child is affected, is no option ***(chapter 2)***.

Professionals expressed similar positive views towards NIPD as the high-risk couples, and expected that NIPD will increasingly be used by these couples ***(chapter 7)***. Although they had concerns about some technical and practical aspects, such as the possibility of false negative results [30, 31]. In the United Kingdom, NIPD has been available for several years [32]. In contrast to the fast implementation of non-invasive prenatal testing (NIPT) for fetal aneuploidy screening that is offered to all pregnant women [33], NIPD is not yet implemented in Dutch healthcare although a pilot study is being performed [28, 34]. One explanation for the delay may be the smaller demand, since it mainly benefits couples with a known increased risk. Professionals addressed in this thesis say that implementation of NIPD lacks the priority and resources necessary to organise and implement such a test. However, given our results indicating high

willingness to use NIPD by both couples and professionals, I am convinced that NIPD will likely soon become standard practice, despite current challenges.

Germline genome editing: the distant future or a not yet imaginable era

Germline genome editing (GGE) involves making genetic changes to germ cells or early-stage embryos. Currently, GGE is prohibited worldwide, although it is increasingly being seen as acceptable in some circumstances. ***Chapter 6*** presents an overview of reasons in favour and against clinical implementation of GGE. A total of 169 reasons were identified from literature: 90 in favour and 79 against. Reasons were grouped into 13 domains including safety, quality of life, costs, and parental rights and duties [35]. Arguments against clinical implementation of GGE included the potential use for enhancement, i.e. introduction of changes in the genome to improve or select physical characteristics, and slippery slope scenarios, i.e. the belief that allowing GGE would inevitably lead to eugenics and dystopic scenarios like the creation of designer babies. Arguments against GGE were emphasized, especially since GGE impacts future generations. The most mentioned argument in favour or GGE was that it could prevent suffering of the child and the parents by curing a genetic disease. The argument of parental responsibility, of wanting the best for your child, is transformed in the current debate around GGE due to heritable changes to potential future generations, and thus decisions have consequences for others as well.

The investigation outlined in ***chapter 2*** showed that although high-risk couples share concerns regarding the creation of "designer babies", i.e. a child whose genome is edited with selected non-medical traits, they were generally more positive towards GGE than the general public, possibly due to an experiential perspective towards living with a severe genetic disorder[16]. Similar to other studies [36, 37], couples reckoned that fewer embryos will be discarded if GGE is used instead of PGT, which was considered a positive aspect. The possibility of increasing PGT efficiency when combined with GGE was mentioned by professionals and reviewed literature in this thesis, as well as in other studies [36, 38-40]. On the other hand, some professionals in ***chapter 7*** argued that we should not invest in GGE since for the large majority of couples PGT is an established available alternative ***(chapter 7)***. Professionals also pointed to the strict legislation around embryo research, for example, it is not allowed to culture embryos for scientific research beyond 14 days in the Netherlands (Embryowet) [41]. According to some, this strict legislation hinders further development of GGE. The sustainability of the legislation in place is currently being evaluated in the Netherlands [42]. Previous debates on the development and implementation of new genetic technologies were highly similar. For instance, arguments

concerning PGT showed similar pros and cons [32,33], including its safety and reliability [43, 44]. PGT is now an established medical procedure, with a cumulative number of 1080 live births since 1995 after a PGT procedure calculated in the year 2019-2020 [45].

Scientific development is moving towards clinical application of GGE. The discovery of the game-changing gene-editing technology CRISPR-Cas in 2012 has dramatically enhanced the GGE possibilities and ignited fierce ethical debates. In November 2018, the first genome-edited babies were born in China, generating heavy criticism [46]. The urgency of determining whether and how GGE could be ethically acceptable is increasing, and experts have called for public engagement [43, 47]. We conducted a survey study in January 2018 among the Dutch general public to examine the viewpoints concerning GGE ***(chapter 5)***. Our results showed that the acceptability of GGE for other couples to modify their embryo (22.8%) was higher than the willingness to use GGE (17.4%) among the Dutch general public [48]. Of the participants 28% knew someone with a genetic condition, which may have supported their views regarding GGE as acceptable. Our results are in line with previous studies that assessed public acceptability of GGE in Japan [49], United States [50, 51], United Kingdom, Canada and Australia [51]. Acceptability of GGE depended on certain conditions, such as the availability of an alternative procedure, like PGT [52, 53]. When alternative procedures are not available, our investigation showed that potential safety risks had the largest impact on whether the public supported GGE, followed by effectiveness of the treatment. The indication for GGE i.e. a medical indication for disease prevention or a non-medical enhancement indication had an effect on the acceptability by the general population. Application of GGE for preventing disease purposes was highly favoured. However, in a context without alternative procedures available for GGE and provided that there is a substantial benefit to the well-being of the future child the general public was slightly more tolerant of enhancement, like a desirable characteristic such as longevity. This aspect needs further research because our study investigated this in a context without alternative procedures. This perspective of the general public did not reflect the arguments identified in our review. It was also different from professionals' perspectives who argued that if GGE would become safe, it should be used for the prevention of genetic conditions, and not/never for enhancement applications. The possible inequity of access regarding GGE was raised in this thesis, as not all people will be able to afford the technology [54, 55]. High-risk couples mentioned that the technology could be misused to generate profit instead of to provide benefits ***(chapter 4)***. This was also one of the arguments identified against clinical implementation of GGE.

Somatic gene editing: great promise, but not expected to impact reproductive decision making

After birth, some infants with monogenic conditions could profit from somatic gene editing (SGE) as a treatment. SGE uses similar genome editing technologies as GGE, but only modifies cells in the body (somatic) and do not affect germ cells. Our research revealed both couples and professionals said they found it difficult to imagine what the role of SGE would be in the practice of reproductive decision making. Couples with an increased risk argued that they would prefer to have a healthy baby from the start, and thus would opt for options such as PND and PGT, even if an effective gene therapy treatment would be possible in the future ***(chapter 2)***. This contradicts with a systematic literature review, that analysed reproductive decision-making of high-risk couples, which found that the treatability of a condition impacts couples' reproductive decision making [56]. Those couples also argue that they prefer to carry the burden of treatments and tests themselves instead of burdening the future child. In contrast to GGE, somatic gene editing had less opposition among our participants, similar to a study exploring attitudes of German medical students [57]. I conclude that positive views towards SGE as a treatment for affected children probably does not change the preference of prospective parents for PND or PGT.

Dynamics between current and potential future technologies

The results of our investigations detailed in this thesis showed that there are different scenarios conceivable in terms of possible shifts and uptake of the different reproductive genetic technologies discussed. If expanded carrier screening becomes more widespread, more couples with an increased risk of having an affected child would be identified. Would preimplantation genetic testing (PGT) in its current capacity be sufficient for a possible growing demand? It is also expected that increasing identification of carrier couples will increase the demand for non-invasive prenatal diagnosis (NIPD), and the call for its implementation into routine healthcare will thus become more urgent. With or without implementation of ECS in national care, it is expected that NIPD will become a routine diagnostic test in the near future, as is now seen in the United Kingdom [30].

As mentioned by professionals in this thesis, the boundaries between prenatal aneuploidy screening by non-invasive prenatal testing (NIPT) and mono-genetic diagnostics with NIPD might fade. Indeed, why test for one condition when there is test that includes that condition and hundreds more? The emergence of whole exome or whole genome sequencing to study and detect monogenic disease gains interest, however sequencing the entire genome to diagnose (potential

or likely) pathogenic variants remains challenging [58]. Some predict that, in the future, prenatal whole exome or genome sequencing will be available to all pregnant women to sequence fetal DNA and analyse it for several (esp. monogenic) conditions, once current societal and technical challenges are overcome

The combination of GGE with PGT could mean the transfer of more viable embryos and more opportunities for couples to have a healthy child, as around conception the pathogenic variant could be corrected with GGE. It should be noted that the three rounds of IVF/ICSI cycles for PGT which are reimbursed in the Netherlands do not always result in a pregnancy. The pregnancy rate per unaffected embryo transfer ranges between 28-41% [59]. Moreover, experts stated that we should be careful in viewing GGE as an alternative to PGT, because PGT procedures are still necessary to utilize GGE [60]. Another scenario is that GGE and PGT will be both available to couples.

The importance of pre-test counselling to facilitate informed and autonomous decision making was highlighted throughout this thesis. Professionals working in the field of reproductive and genetic healthcare expected that with new reproductive genetic technologies, such as ECS and NIPD, counselling will need to be adjusted and could become more challenging. Despite the fact that GGE is still far from clinical implementation, when couples have questions about this technology, healthcare providers need be able to answer their questions and provide a clear and factual information. The ongoing evolution of genetic reproductive technology requires considerable flexibility and adaptability among (genetic) counsellors, in addition to ongoing education.

Reflection on methodology and limitations

An overall strength of the studies presented here is that the views of the general population, couples who desire children, genetically high-risk couples, and professionals working in the field are all reflected in this thesis. Because successful introduction of new technologies requires a collaboration between all stakeholders involved, we used the Network of Actors model [61] to identify stakeholders that included a broad range of professionals. The in-depth insights and views presented here provide information on the needs and concerns of prospective parents, high-risk couples and society that can be used to guide further policy making. Another strength is that different research methods were used to explore the broad range of perspectives, including semi-structured interviews, focus groups and questionnaires. With this range of methodologies, triangulation of the generated data was possible, assuring internal reliability. Despite these strengths, completeness can never be guaranteed. One limitation is that participants from the general public represented here were highly

educated. This likely introduced bias. Moreover, our studies were conducted in the Netherlands and therefore may not be generalizable. There are other limitations in generalizing some viewpoints presented here. The views of relatives of MPS-III patients on ECS reflected in ***chapter 3*** could be different than relatives of children with other, less severe, genetic conditions. The majority of the study population of chapter 4 that participated in ECS had an a priori high risk. Moreover, selection bias could have occurred when selecting and recruiting the professionals interviewed in ***chapter 7***. We might have selected the professionals that were known to the researchers and thus the opinions might not reflect ones of professionals randomly selected.
This study compared perspectives on available technologies with hypothetical scenarios (e.g. the availability of GGE). When the technologies are introduced in practice, the actual uptake of high-risk couples and the general public might deviate from their stated intended willingness to use these technologies, also known as the intention-behaviour gap [62].

Implications and recommendations for practice and further research
When considering the implementation of new technologies, there are certain prerequisites and steps that need to be taken before such technologies can be used by prospective recipients (i.e. the general public, high-risk couples, professionals). One prerequisite is that there should be a clear demand for the technology within society. Healthcare professionals should be trained according to the most recent insights, and the organisation of care such as sufficient and informed counselling practises should be ensured. All eligible couples should have equal access to the available technologies, which is influenced by costs and reimbursement, but also by the awareness that such tests/technologies exist and the extent of whether people understand the necessary information. Based on the findings in this thesis, several recommendations for shaping the practice of care and policy making involving reproductive genetic technologies can be made:

- *Increasing awareness of tests and general genetic knowledge*. More awareness of existing technologies and more genetic knowledge in general should be generated among professionals and the general public to improve the genetic literacy, at least to the extent to which individuals can obtain and understand information about genetics that affects their lives [63]. Couples who are unaware of the existence of (new) reproductive genetic technologies should be informed about them so they can make more informed decisions. A promising example is the governmental program "Kansrijke Start" [64],

that is planning to invest in the health and well-being of (future) parents and their children before pregnancy.

- *Collaboration between stakeholders*. Professionals working in the field, such as health care providers, ethicists and policy-makers, should continue collaborating and working together across disciplines. The general public and prospective parents should also be included in this collaboration, because only then a full and responsible integration of new technologies will be reached. This thesis shows that perspectives between stakeholders can be similar, but also have important differences. Whereas professionals emphasize technological and practical characteristics of technologies, the views of couples with an increased risk on having an affected child and the general public focus are shaped more by their personal experiences or moral considerations. Responsible implementation requires the joint effort of all stakeholders involved.

- *Continuation of public dialogue*. Ongoing dialogue with the public about reproductive genetic technologies is needed. Especially in the case of GGE, which can affect future generations. Insights into the desirability and demand of new technologies among society are crucial. A successful example is the Dutch DNA-dialogue project, which took place in the Netherlands in 2019 -2020 [65]. These types of dialogues should continuously take place, especially when new technologies come to light.

- *Lessons learned should facilitate current implementation practises*. Lessons learned from existing implementation processes of genetic technologies in the Netherlands (like NIPT) or internationally (like ECS) should be used to facilitate responsible implementation of new reproductive genetic technologies. During the implementation process of NIPT in the Netherlands, a learning phase was created. NIPT was first implemented in a research setting (TRIDENT studies) and a national consortium was established with experts from the field. This learning phase led to responsible and careful implementation [33, 66]. For ECS, lessons can be learned from Australia's Mackenzie's Mission, a pilot study where a test panel of 1300 genes was offered to 10,000 couples, reimbursed by the federal government [67]. These insights can be used to design and further draft governance structures.

Concluding remarks

Rapid scientific advances driving new reproductive genetic technologies will shift the existing balance of available techniques. The perspectives collected in this thesis assist in clarifying our collective views in order to guide policy making and regulations. Couples with an increased risk of having an affected child with a genetic disorder are generally positive towards (new) reproductive genetic technologies. The considerations of couples who reason from an experiential perspective regarding the hypothetical use of new technologies are reflected in underlying concepts such as their own personal values and invasiveness of the technologies. The general public emphasized the importance of equal access to new reproductive genetic technologies. Professionals working in the field of reproductive medicine and genetics highlighted practical considerations, such as the need to prove new technologies are safe. Currently available techniques, like PGT and NIPT, are considered stepping stones and good examples of how new technologies can be responsibly implemented in the future. Professionals expect that NIPD will be available in the next few years, and anticipate more availability and higher uptake of ECS in the near future. All stakeholder groups believed that awareness concerning genetics and the reproductive genetic technologies should and will grow. Moreover, the shift in use from specific high-risk populations to the general population brings along new challenges such as the lack of awareness concerning general genetic reproductive risks, limited perceived personal relevance and low perceived personal risks. At all times, couples should be supported in making autonomous informed decisions. Technologies, like PGT and PND, that were once considered ethically challenging, are now widely used. The Netherlands has experience with responsible implement different technologies (e.g. PGT and NIPT) this is of value for the implementation of new technologies in the future. Related to this, themes like medicalisation of pregnancy and the creation of "designer babies" tend to reoccur as new technologies are introduced. Although these themes are familiar, they should still be scrutinized by continuously engaging prospective parents and the general public in the discussions. The perspectives of stakeholders reflected in this thesis provide valuable insights into the desirability, demands, support and arguments in favour or against the implementation of (new) reproductive genetic technologies. Old questions will have new relevance for future generations of prospective parents facing new technological possibilities.

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CHAPTER 9

Summary
Samenvatting

The field of reproductive genetic technology is changing rapidly due to the introduction of new technologies and the widening scope of currently available tests. These developments challenge current policy and standards of care, and might impact the reproductive decision-making process itself.

In the Netherlands, couples with a known increased risk of having a child with a genetic condition currently have several options available if they want to avoid the birth of an affected child. Among others they can opt for prenatal diagnosis (PND), where the fetal DNA is tested during pregnancy and, if the fetus is affected, couples can decide to terminate the pregnancy or prepare for a child with the genetic disorder. In addition, couples can opt for preimplantation genetic testing (PGT), in which the oocytes are fertilized by in vitro fertilization (IVF) /intracytoplasmatic sperm injection (ICSI) in the laboratory. After genetic testing on a single cell or a few cells of the embryo, an unaffected embryo is eligible for transfer into the uterus.

New technologies are on the horizon; such as non-invasive prenatal diagnosis (NIPD) that is likely to become available in the (near) future and currently conducted as part of a pilot study the Netherlands. The implementation of germline genome editing (GGE) is still far away from clinical use. Currently, this technology is prohibited worldwide and, in the Netherlands, research on embryos is subject to strict regulation. Availability of somatic gene editing (SGE) after the birth of an affected child is also a future technology that could impact reproductive decision making before pregnancy.

Couples can be informed about their risk of having affected offspring at different stages in time: after the birth of an affected child, during pregnancy when congenital anomalies are seen by ultrasound examination, or when prenatal diagnostic testing confirms a genetic diagnosis. Preconception carrier screening enables couples to obtain information about a possible increased risk of having a child with a recessive disorder before pregnancy, which allows for a wider range of reproductive options than testing performed after conception. Expanded carrier screening (ECS) test panels allow screening for multiple conditions concurrently, enabling the possibility of a universal offer for all couples planning a pregnancy. In the Netherlands, apart from ECS offers at two academic hospitals, carrier screening for the general population is not yet implemented in nationwide healthcare.

This thesis explored the dynamics of currently available and evolving reproductive and genetic technologies by examining the perspectives of various stakeholders with the aim of attuning responsible implementation. Responsible implementation of new reproductive genetic technologies requires a thorough reflection on desirability, demand and values. This thesis therefore aimed to gain more

insight into the views on current and potential reproductive technologies of four relevant stakeholder groups: couples with an increased risk of having offspring with a genetic condition, couples who want to have children, the general public and professionals working in the field of reproductive and/or genetic medicine.

Chapter 1 introduced the topics and technologies discussed in this thesis and presents the aim: to gain more insight into the perspectives of a broad variety of stakeholders on the development, desirability, (further) implementation, and expected dynamics of current and possible future reproductive genetic technologies.

The views of couples with an increased risk of having affected offspring on currently available technologies (PND and PGT) and possible future reproductive genetic technologies (NIPD and GGE) are explored in **chapter 2**. Their opinions regarding the possible influence of SGE on reproductive decision making were also explored. Twenty-five semi-structured interviews were conducted in 2018 with couples who all had received genetic counselling on PND and PGT because of their increased risk. Concerns participants mentioned regarding the hypothetical use of the new techniques were similar to previous issues raised in the past about techniques now currently considered routine. These views were shaped by underlying concepts, such as safety aspects, perceived burden of the specific technologies, and moral considerations including attitudes towards abortion. Generally, participants were positive about NIPD because it is considered safer for mother and child compared to prenatal invasive diagnostic methods. GGE was believed to offer increased possibilities over PGT since it is expected that more embryos will be eligible for transfer and, as a consequence, possibly less IVF/ICSI cycles would be needed. Although participants had concerns, for example about GGE's safety, they seemed generally positive because it could broaden their reproductive possibilities. SGE, as a possible future gene therapy for affected children, was not preferred over choosing between the reproductive options to prevent the birth of an affected child such as PND and PGT. Couples indicated that they preferred to carry the burden accompanied with these techniques themselves instead of burdening their future child. Overall, the considerations of couples regarding the future use of genetic technologies remain the same in essence, however with the expected growing number of options and possible shifts in use, users' perspectives should continuously be addressed and understood in order to successfully guide informed decision making as technologies evolve.

Chapter 3 studied the attitudes and perspectives on preconception expanded carrier screening (ECS) of 23 relatives (parents and other family members) of children with mucopolysaccharidosis type III (MPS III, also called Sanfilippo syndrome), which is a severe metabolic disorder, and 18 participants from the general public. Seven focus groups were held in 2019 to enable a group discussion that gave valuable insights into participants' feelings, motives and reactions. Five themes emerged from the data: (i) benefits of ECS, (ii) barriers to opt for ECS, (iii) disclosure of test results (offering a choice), (iv) severity of the disorder as a key criterion for inclusion in ECS test panels, and (v) support for ECS. Both relatives and individuals from the general population supported an offer of ECS to all prospective parents in the Netherlands. There was confusion about the purpose of the test, and ECS was confused with prenatal Down syndrome screening. Only the relatives of MPS-III patients mentioned the benefits of carrier screening for other family members, as severe recessive conditions have an impact on the family as a whole. Several barriers to the implementation of ECS were mentioned, such as the costs of the test, a lack of awareness about the test availability and lack of genetic knowledge in general. Full disclosure of individual test results, instead of reporting couple-based test results only, was preferred. However, participants suggested giving (prospective) parents a choice. Participants of the focus groups supported arranging campaigns that can promote public awareness of ECS. Individuals from the general population more often classified disorders as severe and suitable to include in ECS panels compared to relatives of MPS III patients. This can be attributed to the influence of experiential knowledge, i.e. knowledge of genetic disorders because of personal experience. Both groups supported further implementation of ECS for severe, early-onset disorders. Participants indicated that the concept of ECS is difficult to grasp and awareness of the test low. In order to ensure informed decision making, prospective parents should be educated on the concept of ECS and the type of disorders included through adequate counselling.

The experiences of participants with an expanded carrier screening (ECS) test for 50 severe autosomal recessive disorders, offered in a non-commercial hospital setting, were evaluated in **chapter 4**. The test was available for high-risk couples and members of the general population who were planning a pregnancy. A mixed-method parallel design was used to evaluate the ECS test with questionnaires, and semi-structured interviews were conducted. Twenty-seven carriers and no carrier couples were identified among those who participated in this study. The majority of respondents (86%) made an informed decision to opt for the ECS test, suggesting that counselling and information protocols were

sufficient. The waiting time for test results (mean 7 weeks) was considered too long, and the costs of the test (650 euros per test) were considered too high. The test did not lead to clinically elevated anxiety levels, however, respondents with an a priori high risk based on positive family history, consanguinity, ancestry and/or geographical background and pregnant respondents experienced slightly more anxiety while waiting for the test results. Distress was on average higher for carriers compared to non-carriers, although not clinically significant. Respondents were satisfied with the test: all would opt for the test again and 80% would recommend it to others. To minimize anxiety, it was concluded that the ECS test should ideally be offered before pregnancy. To ensure equal access, out-of-pocket costs should be reduced. The findings are relevant for further implementation of ECS tests and other carrier screening initiatives.

Chapter 5 quantified the perspectives of the Dutch general public on the extent to which GGE is deemed acceptable. A vignette-based survey was disseminated in 2018, and in total 1136 questionnaires were returned. Key aspects of GGE that were incorporated in the vignettes were: (i) its effect on well-being of the future child, (ii) its purpose (for treating disease or non-medical enhancement), (iii) the potential risks for the future child, (iv) its effectiveness (here defined as the chance of a live birth, assuming that if the GGE was not successful, the embryo would not be transferred), (v) the costs, and (vi) the availability of alternative treatments/procedures to prevent the genetic disease (i.e. PGT). The Dutch general public's acceptability of GGE was higher than their own willingness to use GGE. The safety risk of GGE for the future child, followed by effectiveness, had the largest effect on support for GGE, if no alternative was available. In a context without alternative procedures for GGE and provided that there is a substantial benefit to the well-being of the future child the general public is slightly more tolerant of enhancement (like a desirable characteristic such as longevity). In general, participants were strikingly risk-averse, in that they weighed the risks of GGE more heavily than its benefits. If sufficiently proven safe and effective, the public may approve of using GGE instead of solely PGT to prevent disease. These results can contribute to future considerations on the ethics and governance of GGE.

A systematic literature review was conducted to identify arguments in favour and against the clinical implementation of GGE, as described in **chapter 6**. The literature was assessed between 2011 and 2016, and 180 articles were included. A total of 169 reasons were identified, of which 90 reasons were in favour of and 79 against the clinical application of GGE. The reasons could be catego-

rized into 13 domains: (i) quality of life of affected individuals, (ii) safety, (iii) effectiveness, (iv) existence of a clinical need or alternative, (v) costs, (vi) homo sapiens as a species, (vii) social justice, (viii) potential for misuse, (ix) special interests, (x) parental rights and duties, (xi) comparability to acceptable processes, (xii) rights of the unborn child, and (xiii) human life and dignity. The most frequently mentioned reason for the introduction of GGE into the clinic was that it could prevent suffering. The most frequent argument against was that it could introduce safety risks for the child and subsequent generations due to off-target and other unknown genetic (side) effects. At the core of many reasons was the importance of genetic (biological) parenthood for prospective parents. Whether donor gametes or adoption are reasonable alternatives for GGE warrants further study. Authors expressed the need to involve both experts and non-experts in an open discussion. Regulation should be flexible to adapt to evolving technologies, and further analysis of the regulatory process of GGE is recommended.

The perspectives of professional stakeholders working in the field of reproductive and/or genetic medicine towards the possible implementation of new reproductive technologies was presented in **chapter 7**. Implementation of new reproductive genetic technologies requires healthcare professionals to adapt to the new situation. Perspectives on the changing reproductive genetic landscape and expectations for the future were gathered by conducting semi-structured interviews with 21 professionals. All professionals referred to the "typical Dutch approach" when discussing the introduction of new reproductive genetic technologies. This was characterized by support for people living with disabilities and the value of an egalitarian society, limited commercialisation, restrictive legislation and cautiously integrating new technologies in clinical care. Different scenarios for embedding ECS in future practice were envisioned, implementation of NIPD in practice was considered evident, and views on GGE varied. Stakeholders mentioned that previous implementation of technologies in the Netherlands is characterized by collective learning phases and careful introduction. Although stakeholders mention their interest in innovation, this process could be delayed by the legislative framework. **Chapter 7** described how the international trends and advances of technologies are expected to manifest itself in a national setting.

Chapter 8 discussed the general findings from the different chapters, including research methodologies used in this thesis, and provided recommendations for current practice and future research.

Rapid scientific advances driving new reproductive genetic technologies will shift the existing balance of available techniques. The perspectives of stakeholders involved with these currently available (e.g. PGT) and possibly future available (e.g. NIPD) technologies constitute a valuable body of research on the underlying opinions, beliefs and values that can be used to assist in drafting appropriate policy and regulations guiding responsible implementation of new reproductive genetic technologies. This thesis shows the value of elucidating the views of stakeholders involved and stresses the importance of continuously engaging prospective parents and the general public in the discussions.

Samenvatting

De velden van reproductieve en genetische gezondheidszorg zijn aan snelle verandering onderhevig door de introductie van nieuwe technologieën en de toenemende reikwijdte van de huidig beschikbare testen. Deze ontwikkelingen vormen een uitdaging voor het hedendaagse beleid en de zorg en kunnen daarnaast van invloed zijn op het reproductieve besluitvormingsproces van paren en de voorlichting van zorgprofessionals.

Op dit moment hebben paren, met een bekend verhoogd risico op een kind met een ernstige erfelijke (genetische) aandoening, in Nederland verschillende opties tot hun beschikking als het gaat om het krijgen van kinderen. Zij kunnen onder andere kiezen voor prenatale diagnostiek (PND), waarbij foetaal DNA na een vlokkentest of vruchtwaterpunctie wordt getest tijdens de zwangerschap. Daarna kunnen paren kiezen, als de foetus de betreffende aandoening heeft, om de zwangerschap af te breken of om zich voor te bereiden op een kind met de betreffende genetische aandoening. Daarnaast kunnen koppels kiezen voor een preïmplantatie genetische test (PGT) waarbij eicellen worden bevrucht door in-vitrofertilisatie (IVF)/intracytoplasmatische sperma-injectie (ICSI) in het laboratorium. Na een genetische analyse van een enkele cel of cellen van het embryo, komt alleen een niet-aangedaan embryo in aanmerking voor terugplaatsing in de baarmoeder.

Nieuwe technieken zijn in aantocht en vergroten de reproductieve opties voor aanstaande ouders, zoals niet-invasieve prenatale diagnostiek (NIPD). Op basis van onderzoek naar celvrij DNA in het bloed van een zwangere vrouw, kunnen hiermee aandoeningen worden geïdentificeerd die veroorzaakt worden door varianten in één gen. Deze techniek heeft in tegenstelling tot PND, geen miskraamrisico.

Kiembaanmodificatie is een techniek waarbij het DNA van kiembaancellen of embryo's kan worden aangepast. Op deze manier zouden ernstige erfelijke (genetische) aandoeningen in de toekomst mogelijk kunnen worden 'gerepareerd'. Omdat deze DNA-aanpassingen gedaan worden in de kiembaan worden deze doorgegeven aan het toekomstig nageslacht. Momenteel is deze technologie wereldwijd verboden en is onderzoek op embryo's in Nederland aan strenge regelgeving onderhevig. De beschikbaarheid van somatische gentherapie, na de geboorte van aangedane kinderen, is daarentegen minder beladen omdat met deze techniek de genaanpassingen worden gedaan in somatische cellen en deze niet worden doorgegeven aan het nageslacht. Implementatie en beschikbaarheid van somatische gentherapie kan de reproductieve besluitvorming vóór de zwangerschap mogelijk beïnvloeden.

Paren met een kinderwens kunnen op verschillende momenten geïnformeerd worden over hun verhoogde kans op het krijgen van een (volgend) kind met een erfelijke of genetische aandoening. Namelijk: na de geboorte van een aangedaan kind, tijdens de zwangerschap wanneer aangeboren afwijkingen worden vastgesteld, bijvoorbeeld door middel van echografisch onderzoek, of wanneer prenatale diagnostiek een genetische aandoening bevestigt of ontdekt. Preconceptionele dragerschapsscreening stelt paren in staat om informatie te verkrijgen over een mogelijk verhoogd risico op het krijgen van een kind met een recessieve aandoening vóór de zwangerschap. Hierdoor kunnen paren al vóór de zwangerschap een keuze maken uit verschillende reproductieve mogelijkheden. Technologische ontwikkelingen maken screening op tientallen tot duizenden aandoeningen tegelijk mogelijk waardoor een universeel aanbod uitvoerbaar is voor alle paren met een kinderwens. In Nederland is er, afgezien van twee academische ziekenhuizen die een brede dragerschapstest aanbieden voor 50-70 genen, geen landelijk aanbod beschikbaar voor dragerschapsscreening voor de algemene bevolking.
Dit proefschrift onderzocht de dynamiek van de bestaande en in ontwikkeling zijnde reproductieve en genetische technologieën door middel van het in kaart brengen van de perspectieven van verschillende betrokkenen met als doel het afstemmen van een verantwoorde implementatie. Verantwoorde implementatie van nieuwe technologieën vereist een grondige reflectie van betrokkenen op de vraag naar deze technieken, de wenselijkheid en bijbehorende waarden. Dit proefschrift had daarom als doel om meer inzicht te krijgen in de opvattingen over huidige en mogelijk toekomstige reproductieve technologieën van vier relevante groepen stakeholders, namelijk: paren met een verhoogd risico op het krijgen van een kind met een erfelijke/genetische aandoening, paren met een kinderwens, mensen uit de algemene bevolking en deskundigen of zorgprofessionals die werkzaam zijn in het veld van reproductieve en/of genetische gezondheidszorg.

Hoofdstuk 1 introduceert de onderwerpen en technieken die in dit proefschrift worden besproken en presenteert het doel van het proefschrift: meer inzicht verkrijgen in de perspectieven van een breed scala aan stakeholders op de ontwikkeling, wenselijkheid, (verdere) implementatie en verwachte dynamiek tussen huidige en mogelijk toekomstige reproductieve genetische technologieën.

De opvattingen van paren met een verhoogd risico op het krijgen van een aangedaan kind ten aanzien van de huidig beschikbare technologieën (PND en PGT) en de mogelijk toekomstige reproductieve genetische technieken (NIPD en kiembaanmodificatie) worden onderzocht in **hoofdstuk 2**. Hun opvattingen over de

mogelijke invloed van somatische gentherapie op de reproductieve besluitvorming zijn ook in kaart gebracht. In 2018 zijn er vijfentwintig semigestructureerde interviews afgenomen met paren die, vanwege hun verhoogde risico, eerder al genetische counseling over PND en PGT hadden ontvangen. De zorgen die deelnemers uitten over het (hypothetische) toekomstige gebruik van de nieuwe technieken waren vergelijkbaar met eerdere zorgen die in het verleden werden geuit over technieken die nu als routine worden beschouwd (zoals prenatale diagnostiek). Deze opvattingen werden gevormd door onderliggende concepten zoals veiligheidsaspecten, ervaren belasting van de technieken in kwestie en morele overwegingen waaronder de houding ten aanzien van het afbreken van de zwangerschap. Over het algemeen waren de geïnterviewde paren positief over NIPD omdat het als veiliger wordt gezien voor moeder en kind in vergelijking met invasieve prenatale diagnostiek. Er werd verondersteld dat kiembaanmodificatie meer te bieden heeft dan PGT, omdat verwacht wordt dat er meer embryo's in aanmerking komen voor terugplaatsing en als gevolg daarvan mogelijk minder IVF/ICSI-cycli nodig zullen zijn. Hoewel paren zich bijvoorbeeld zorgen maakten over de veiligheid van kiembaanmodificatie waren ze nog wat terughoudend, maar leken ze over het algemeen voorzichtig positief over deze techniek, omdat het hun reproductieve mogelijkheden zou kunnen vergroten. Somatische gentherapie, als een mogelijk toekomstige therapie voor aangedane kinderen, had niet de voorkeur boven reproductieve opties voor of tijdens de zwangerschap, zoals PGT en PND. Paren gaven aan liever zelf de last van deze techniek te dragen dan hun toekomstige kind te belasten. De resultaten suggereren dat de overwegingen van paren met betrekking tot het toekomstige gebruik van genetische technologieën nagenoeg hetzelfde blijven. Met het verwachte groeiende aantal opties en mogelijke verschuivingen in het gebruik is het van belang om de perspectieven van gebruikers blijvend in kaart te brengen, zodat gedurende deze technologische ontwikkelingen, de geïnformeerde besluitvorming kan worden gefaciliteerd.

Hoofdstuk 3 beschrijft de houdingen tegenover en perspectieven op brede dragerschapsscreening van familieleden (ouders en andere familieleden) van kinderen met mucopolysaccharidose type III (MPS III, ook wel Sanfilippo-syndroom genoemd), een ernstige recessief erfelijke stofwisselingsstoornis, en van mensen uit de algemene bevolking. In 2019 werden vier focusgroepen gehouden met 23 familieleden en drie focusgroepen met 18 mensen uit de algemene bevolking. Er werd gekozen voor focusgroepen om een groepsdiscussie mogelijk te maken om waardevolle inzichten te verkrijgen in de gevoelens, motieven en houding van de deelnemers. Vijf thema's kwamen naar voren: (i) de voordelen van preconceptionele dragerschapsscreening, (ii) belemmeringen om gebruik te maken van de test,

(iii) terugkoppeling van de testresultaten, (iv) ernst als belangrijkste criterium om screening panels samen te stellen, (v) draagvlak voor implementatie. Zowel familieleden als mensen uit de algemene bevolking steunden het beschikbare aanbod van brede dragerschapsscreening aan alle paren in Nederland met een kinderwens vanuit twee academische centra. Er was verwarring over het doel van de test en brede dragerschapsscreening werd verward met andere testen zoals prenatale screening voor downsyndroom. Alleen familieleden van mensen met MPS-III benoemden de voordelen van dragerschapsscreening voor andere familieleden, aangezien ernstige recessieve aandoeningen een impact hebben op het hele gezin/familie. Verschillende belemmeringen voor de implementatie en het gebruik van de brede dragerschapstest werden genoemd, zoals de kosten van de test, een gebrek aan bewustzijn over de beschikbaarheid van de test en een gebrek aan kennis over genetica in het algemeen. De terugkoppeling van de individuele test resultaten, in plaats van alleen de koppel uitslag, had de voorkeur. Deelnemers stelden echter voor om paren met een kinderwens een keuze te geven. Focusgroep deelnemers ondersteunden het opzetten van campagnes die het publieke bewustzijn over de brede dragerschapstest zou kunnen bevorderen. Individuen uit de algemene bevolking classificeerden aandoeningen vaker als ernstig en geschikt om op te nemen in de testpanels in vergelijking met familieleden van MPS-III patiënten. Dit kan worden toegeschreven aan de invloed van ervaringskennis, dat wil zeggen kennis van genetische aandoeningen door persoonlijke ervaring. Deelnemers steunden verdere implementatie van de brede dragerschapstest voor ernstige, vroeg in het leven optredende aandoeningen. Deelnemers gaven aan dat het concept van brede dragerschapsscreening moeilijk te vatten is en bewustzijn over de test laag. Om geïnformeerde besluitvorming te bewaken moeten toekomstige ouders voorgelicht worden over de brede dragerschapstest en het soort aandoeningen die zijn geïncludeerd door middel van adequate counseling.

De ervaringen van deelnemers aan een brede dragerschapstest voor 50 ernstig autosomaal recessieve aandoeningen, aangeboden in één van de twee academische centra, werden geëvalueerd in **hoofdstuk 4**. De test was zowel beschikbaar voor paren met een kinderwens met een a priori hoger risico op het krijgen van een kind met een recessieve aandoening, zoals door consanguïniteit (bloedverwantschap), afkomst en/of geografische achtergrond en een positieve familieanamnese, als voor paren uit de algemene bevolking. Een mixed-methods methode werd gebruikt om het aanbod en gebruik van de dragerschapstest met vragenlijsten te evalueren en er werden zestien semigestructureerd interviews afgenomen. Onder de 86 deelnemers aan de test die de vragenlijst hadden inge-

vuld waren 27 dragers en geen dragerparen. De meerderheid van de deelnemers (86%) maakte een geïnformeerde beslissing om voor de brede dragerschapstest te kiezen, wat suggereert dat de counseling en informatie voldoende was, echter ging het wel om overwegend hoogopgeleide deelnemers en om mensen die zichzelf hadden aangemeld voor de test. De wachttijd voor ontvangst van de testresultaten (gemiddeld 7 weken) vond men te lang en de kosten voor de test (650 euro per test) te hoog. Deelname aan de test leidde niet tot een klinisch verhoogd angstniveau gemeten met de State-Trait Anxiety Inventory (STAI), maar deelnemers met een a priori hoog risico en zwangere deelnemers ervoeren iets meer angst tijdens het wachten op de testresultaten. Stress, gemeten met de Impact of Event Scale (IES) was over het algemeen hoger voor dragers dan voor niet-dragers, hoewel niet klinisch significant. Deelnemers waren tevreden met de test: iedereen zou opnieuw voor de test kiezen, inclusief alle dragers, en 80% zou anderen aanraden om ook de test te doen. Om angst en zorgen te minimaliseren zou de brede dragerschapstest bij voorkeur vóór de zwangerschap moeten worden aangeboden. Daarnaast zouden paren met a priori hoger risico intensievere begeleiding geboden moeten worden om stress te minimaliseren en eventueel enkel een koppel-uitslag (in plaats van individueel) aanbieden. Om gelijke toegang te garanderen, moet de eigen betaling worden verlaagd. De bevindingen zijn relevant voor de verdere implementatie van brede dragerschapstesten en andere initiatieven op het gebied van dragerschapsscreening.

Hoofdstuk 5 kwantificeert de perspectieven van de algemene Nederlandse bevolking op de mate waarin kiembaanmodificatie aanvaardbaar wordt geacht. In 2018 is een op een vignette (gebruik van scenario's) gebaseerde vragenlijststudie verspreid onder 1857 mensen uit een representatief panel voor de volwassen Nederlandse bevolking. Er zijn in totaal 1136 vragenlijst geretourneerd. Belangrijke aspecten van kiembaanmodificatie, die in de vignetten zijn verwerkt, waren: (i) het effect op het welzijn van het toekomstige kind, (ii) het doel van de toepassing; behandeling van ziekte of niet-medische mensverbetering/enhancement, (iii) de mogelijke risico's voor het toekomstig kind, (iv) de effectiviteit, gedefinieerd als de kans op een levend geboren kind, ervan uitgaande dat als de kiembaanmodificatie niet zou slagen, het embryo niet zou worden teruggeplaatst, (v) de kosten, en (vi) de beschikbaarheid van alternatieve behandelingen/procedures (PGT) om de genetische aandoening te voorkomen. De aanvaardbaarheid van kiembaanmodificatie onder de respondenten was hoger dan de eigen bereidheid om gebruik te maken van kiembaanmodificatie. Het veiligheidsrisico van kiembaanmodificatie voor het toekomstige kind, gevolgd door effectiviteit, had het grootste effect op de steun van de respondenten voor kiembaanmodifica-

tie, als er geen alternatief beschikbaar was. In een situatie zonder alternatieve procedures voor kiembaanmodificatie en op voorwaarde dat er een substantieel voordeel is voor het welzijn van het toekomstige kind, waren de respondenten iets toleranter voor mensverbetering/enhancement (bijvoorbeeld voor een wenselijk kenmerk zoals een lange levensduur) dan als er wel een alternatief zou zijn. Over het algemeen waren respondenten opvallend risicomijdend, in die zin dat ze de veiligheidsrisico's van kiembaanmodificatie zwaarder wogen dan de voordelen. De resultaten suggereren dat als kiembaanmodificatie voldoende veilig en effectief is, het algemene publiek toestemming zal geven voor het gebruik van kiembaanmodificatie om aandoeningen te voorkomen. De resultaten kunnen bijdragen aan toekomstige ethische en beleidsmatige overwegingen ten aanzien van de klinische toepassing van kiembaanmodificatie.

Een systematische literatuurstudie werd gedaan om redenen voor en tegen de klinische implementatie van kiembaanmodificatie te identificeren, zoals beschreven in **hoofdstuk 6**. De literatuur tussen 2011 en 2016 werd bekeken en er werden 180 artikelen geïncludeerd. In totaal werden er 169 redenen geïdentificeerd waarvan 90 redenen voor en 79 redenen tegen de klinische toepassing van kiembaanmodificatie. De redenen werden onderverdeeld in 13 domeinen: (i) de kwaliteit van leven van aangedane personen, (ii) veiligheid, (iii) effectiviteit, (iv) klinische behoefte aan een alternatief, (v) kosten, (vi) homo sapiens als soort, (vii) sociale rechtvaardigheid, (viii) potentieel voor misbruik, (ix) speciale belangen, (x) ouderlijke rechten en plichten, (xi) vergelijkbaarheid met aanvaardbare technieken, (xii) rechten van het ongeboren kind en (xiii) menselijk leven en waardigheid. De meest genoemde reden voor de introductie van kiembaanmodificatie in de kliniek was dat het leed kan voorkomen. De meest genoemde reden tegen was dat het veiligheidsrisico's voor het kind en volgende generaties zou kunnen hebben vanwege zogenaamde onbedoelde en onbekende bijwerkingen. De kern van veel redenen was het belang van genetisch (biologisch) ouderschap voor aanstaande ouders. Of gebruik van donorgameten of adoptie de voorkeur hebben boven kiembaanmodificatie als dit beschikbaar is, behoeft nader onderzoek. Auteurs in de literatuur spraken de noodzaak uit om zowel experts als niet-experts te betrekken bij een open discussie. De regelgeving moet flexibel zijn om zich aan te passen aan evoluerende technologieën en verdere analyse van het regelgevingsproces van kiembaanmodificatie wordt aanbevolen.

De perspectieven van professionals werkzaam op het gebied van reproductieve geneeskunde en/of genetica, ten aanzien van de mogelijke implementatie van nieuwe reproductieve technologieën werden gepresenteerd in **hoofdstuk 7**. Imple-

mentatie van nieuwe reproductieve genetische technologieën vereist dat professionals in de gezondheidszorg zich aanpassen aan de nieuwe situatie. Perspectieven op het veranderende reproductieve genetische landschap en verwachtingen voor de toekomst werden verzameld door middel van semigestructureerd interviews met 21 professionals, waaronder klinisch en moleculaire genetici, beleidsmedewerkers en onderzoekers. Alle professionals verwezen naar de "typisch Nederlandse aanpak" bij het bespreken van de introductie van nieuwe reproductieve genetische technologieën. Deze typisch Nederlandse aanpak kenmerkt zich door restrictieve wetgeving en voorzichtige integratie van nieuwe technologieën in de klinische zorg, de acceptatie van mensen met een handicap of beperking, de behoefte aan handhaving van de ondersteuning aan deze groep, de waarde van een egalitaire samenleving en beperkte toegestane commercialisering. Er waren verschillende scenario's voor de inbedding van brede dragerschapsscreening in de toekomstige praktijk voorzien, implementatie van NIPD in de praktijk werd voor de hand liggend geacht en de meningen over kiembaanmodificatie liepen uiteen. Professionals gaven aan dat eerdere implementatie van technologieën in Nederland wordt gekenmerkt door collectieve leerfasen en zorgvuldige introductie. Hoewel betrokkenen aangeven geïnteresseerd te zijn in technologische innovatie, zoals van de beschreven reproductieve technieken, wordt dit proces vertraagd door het wetgevingskader. **Hoofdstuk 7** beschrijft hoe de internationale trends en ontwikkelingen van technologieën zich naar verwachting zullen manifesteren in een nationale setting.

Hoofdstuk 8 bediscussieert de algemene bevindingen uit de verschillende hoofdstukken, inclusief de onderzoeksmethodieken die in dit proefschrift zijn gebruikt en dit hoofdstuk geeft aanbevelingen voor de huidige praktijk en toekomstig onderzoek.

Snelle wetenschappelijke voortuitgang werkt als een impuls voor nieuwe reproductieve technologieën. Dit zal het bestaande evenwicht van beschikbare technieken doen verschuiven. De perspectieven van betrokkenen bij deze momenteel beschikbare technologieën (bijvoorbeeld PGT) en mogelijk in de toekomst beschikbare technologieën (bijvoorbeeld NIPD en brede dragerschapstesten), geven waardevolle kennis over de onderliggende meningen, overtuigingen en waarden. Deze kennis kan worden gebruikt om te helpen bij het opstellen van passend beleid en regelgeving die verantwoordelijke implementatie van nieuwe reproductieve genetische technologieën kan bewerkstelligen. Dit proefschrift toont de waarde aan van het verhelderen van de standpunten van de betrokken stakeholders en benadrukt het belang van het voortdurend betrekken van toekomstige ouders en het algemene publiek bij discussies.

ADDENDUM

List of publications
List of contributing authors
PhD Portfolio
Dankwoord/ Acknowledgements
About the author

List of publications

van Dijke, I., Lakeman, P., Mathijssen, I. B., Goddijn, M., Cornel, M. C., & Henneman, L. (2021). How will new genetic technologies, such as gene editing, change reproductive decision-making? Views of high-risk couples. European Journal of Human Genetics , 29(1), 39–50. https://doi.org/10.1038/s41431-020-00706-8

Conijn, T., van Dijke, I., Haverman, L., Lakeman, P., Wijburg, F. A., & Henneman, L. (2021). Preconception expanded carrier screening: a focus group study with relatives of mucopolysaccharidosis type III patients and the general population. Journal of Community Genetics, 12(3), 311–323. https://doi.org/10.1007/s12687-021-00519-2

van Dijke, I., Lakeman, P., Sabiri, N., Rusticus, H., Ottenheim, C., Mathijssen, I. B., Cornel, M. C., & Henneman, L. (2021). Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. European Journal of Human Genetics, 29(8), 1252–1258. https://doi.org/10.1038/s41431-021-00923-9

van Dijke, I., van Wely, M., Berkman, B. E., Bredenoord, A. L., Henneman, L., Vliegenthart, R., Repping, S., & Hendriks, S. (2021). Should germline genome editing be allowed? The effect of treatment characteristics on public acceptability. Human Reproduction, 36(2), 465–478. https://doi.org/10.1093/humrep/deaa212

van Dijke, I., Bosch, L., Bredenoord, A. L., Cornel, M., Repping, S., & Hendriks, S. (2018). The ethics of clinical applications of germline genome modification: a systematic review of reasons. Human Reproduction, 33(9), 1777–1796. https://doi.org/10.1093/humrep/dey257

van Dijke, I., van El, C.G., Lakeman, P., Goddijn, M., Rigter, T., Cornel, M.C., & Henneman, L. (2022) Dynamics of reproductive genetic technologies: perspectives of professional stakeholders. Accepted for publication.

Other publications

Dijke, I., & van EL, C. G. (2019) Kiembaanmodificatie: een medisch ethisch perspectief op paren met een kinderwens. Podium voor Bio-ethiek, 26 (1), 5-7

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PhD Portfolio

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Amsterdam UMC
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PhD period: 2017-2021
Promotors: Prof. dr. Lidewij Henneman, Prof. dr. Martina Cornel
Copromotors: prof. dr. Mariëtte Goddijn, dr. Phillis Lakeman

Training	Year	Workload (Hours/ ECTS)
Presentations and national and international conferences		
Annually Amsterdam Reproduction and Development Symposium (oral presentation)	2017	1.0
WIT Festival/ Wetenschapsfestival AMC (oral presentation)	2017	1.0
Wetenschapsdag Klinische Genetica Amsterdam UMC (oral presentation)	2017	1.0
De Nederlandse Associatie voor Community Genetics en Public Health Genomics (NACGG) (oral presentation)	2017	1.0
Thessaloniki International Conference- Oviedo Convention- Thessaloniki /Greece (oral presentation)	2017	2.0
Mini-symposium for PhD defence Saskia Hendriks, with dr. Robin Lovell-Badge (oral presentation)	2017	1.0
The European Society of Human Genetics conference – Milan / Italy (oral presentation)	2018	2.0
Annual Amsterdam Reproduction and Development Symposium (oral presentation)	2018	1.0
ISPD: International Society for Prenatal Diagnosis Conference – Antwerp / Belgium (oral presentation)	2018	2.0
MFVU congres 'streven naar perfectie' (Workshop and Presentation)	2018	1.0
The European Society of Human Genetics conference – Gothenburg/ Sweden (oral presentation)	2019	2.0

Training	Year	Workload (Hours/ ECTS)
The World Congress on Controversies in Preconception, Preimplantation and Prenatal Genetic Diagnosis (COGEN)- Paris/ France (poster presentation)	2019	2.0
InScience - International Science Film Festival – Nijmegen (debate/ discussion panel)	2019	1.0
De Nederlandse Associatie voor Community Genetics en Public Health Genomics (NACGG) (oral presentation)	2020	1.0
PGD Nederland annual meeting (oral presentation)	2020	1.0
Several presentations about PhD research and journal clubs at departments 'Human Genetics, section Community Genetics' and 'Center for Reproductive Medicine'	2017-2021	2.0
Courses		
Practical Biostatistics (AMC PhD Program)	2017	1.1
Research Integrity	2017	2.0
Basic Medical Statistics Course op NKI, 5 days	2018	2.0
Scientific Writing in English AMC	2018	1.5
Project Management AMC	2018	0.6
Medical Literature Endnote	2018	0.1
Training reducing stress with compassionate mind- for PhD's UvA	2019	0.5
From Pixel to Publication (AMC)	2019	0.8
Workshop: Mixed Classroom	2020	0.1
Workshop: how to make a video with impact	2020	0.1
Workshop: Motiverende gespreksvoering	2021	0.1
Basis Kwalificatie Onderwijs (BKO)	2020-2021	10
Teaching		
Supervision of students with writing Bachelor or Master thesis: Robin Laird, Naoul Sabiri and David Klein	2017-2021	

Training	Year	Workload (Hours/ ECTS)
Tutoring medical students (bachelor)	2019-2021	
Developed and held a lecture in the minor course 'Genetics and Public Health'	2018-2020	0.18*3=0.54
Other activities		
Work Visit at National Institutes of Health (NIH) to Vence Bonham – Washington D.C. / United States Attended meetings, and held presentations	2019	10.0
Board/ Committee member of "Association of Community Genetics and Public Health Genomics (NACGG))" organizing conferences twice a year	2018-2021	2.0
Board member of "Jong Amsterdam UMC" (a platform for young employees) organizing conferences, workshops and network events	2017-2021	2.0
Board member/ PhD representative for Research Institute's PhD council (ProVUmc) - Representative of VUmc for Promovendi Netwerk Nederland (PNN)	2017-2019	2.0
Amsterdam Reproduction and Development retreat committee for PhD& Post-docs	2019	1.0
Part of PhD intervision group (Amsterdam Public Health)	2017-2020	0.5
Grants, I have previously applied for: Simonsfonds (awarded), Lowlands project proposal (rejected), Genootschap ter bevordering van Natuur-, Genees- en Heelkunde travelgrant UvA (rejected), AR&D travelgrant round 2019 (awarded), Dutch L'Oréal-Unesco Rising Talents Prize 2019 with two recommendation letters (rejected).	2018 & 2019	

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Begint het dankwoord van ieder proefschrift niet met ‘alleen had ik het niet gered’? Ik heb lang nagedacht over een originelere openingszin voor mijn dankwoord, maar die kwam er niet. Het is echt zo, alleen had ik het niet gered.

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Lieve papa en mama, jullie oudste dochter (wat Ivy echt?!) gaat promoveren. Wie had dat ooit gedacht, ik in ieder geval niet. Maar dit had ik echt niet zonder jullie gekund. Ik kan mij nog zo goed herinneren dat jullie, op de dag dat ik gebeld zou worden of ik was geslaagd voor mijn havo-diploma, naar het winkeltje kwamen waar ik toen werkte. Het hing erom namelijk of ik zou slagen, de blijdschap en trots die ik op jullie gezichten zag toen het verlossende telefoontje kwam vergeet ik nooit meer. Lieve papa, bedankt voor al je wijze woorden, goede grapjes en eindeloze telefoongesprekken. Je bent de leukste en beste vader die ik mij kan wensen, echt. Lieve Irene, ik ben blij dat papa en jij elkaar hebben leren kennen. Lieve mama, jij ook bedankt voor al je wijze woorden, adviezen over proefschrift gerelateerde zaken of de plantjes in de tuin. Je bent de liefste en beste mama die ik mij kan wensen, echt.

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"Ik ben zo klein, zei de mol.
Ja, zei de jongen, maar je maakt een groot verschil."
-Charlie Mackesy, De jongen, de mol, de vos en het paard

About the author

Ivy van Dijke werd geboren op 27 december 1989 in Rotterdam als oudste in een gezin van vier kinderen. Zij groeide op in Rotterdam en in Den Haag. In 2007 ontving zij haar havo-diploma aan het Haags Montessori Lyceum. Ze vertrok naar Amsterdam om fysiotherapie te gaan studeren aan de Hogeschool van Amsterdam (HvA). Tijdens haar opleiding tot fysiotherapeut liep Ivy onder meer stage in Zambia en volgde zij een aantal vakken van de bacheloropleidingen communicatiewetenschappen en psychologie van de Universiteit van Amsterdam en de Vrije Universiteit. Afgestudeerd in 2012 ging zij aan het werk als fysiotherapeut. Na enige tijd werkzaam te zijn als fysiotherapeut is zij in 2013 begonnen aan de premaster Gezondheidswetenschappen aan de Vrije Universiteit. Hierop volgde de tweejarige master Management, Policy Analysis and Entrepreneurship in Health and Life Sciences. Tijdens deze opleiding liep zij stage bij de non-profitorganisatie Women on Waves waar ze onderzoek verrichtte naar toegang tot abortus wereldwijd en daarna liep ze stage bij Kaleidos Research waar ze onderzoek deed naar de Sustainable Development Goals en het effect hiervan op het Nederlandse gezondheidszorgbeleid. Bij het Koninklijk Instituut voor de Tropen heeft zij haar masterscriptie geschreven over tienerzwangerschappen en vrouwenbesnijdenis. Na haar afstuderen in 2016 is ze gaan werken bij het Athena Instituut als junior onderzoeker en docent. In 2017 is zij gestart als een van de eerste alliantie onderzoekers van het Amsterdam Reproduction and Development research Institute van Amsterdam UMC. Ze werkte bij de sectie Community Genetics van de afdeling: Humane Genetica op locatie VUmc en het centrum voor Voortplantingsgeneeskunde op locatie AMC onder leiding van Prof. Lidewij Henneman, Prof. Martina Cornel, dr. Phillis Lakeman en Prof. Mariëtte Goddijn (het eerste jaar van haar promotietraject was Prof. Sjoerd Repping hier bij betrokken). Tijdens haar promotieonderzoek gaf Ivy onderwijs aan onder andere geneeskundestudenten en was ze actief in het bestuur van de promovendi vereniging van het VUmc van september 2017 tot januari 2020 en is ze vier jaar lang bestuurslid geweest bij Jong Amsterdam UMC.

Momenteel werkt Ivy als wetenschappelijk docent voor de opleiding Medische Informatiekunde aan de Universiteit van Amsterdam, ze begint binnenkort als Beleidsmedewerker Ethiek bij het Ministerie van Volksgezondheid, Welzijn en Sport. Ze woont samen met haar vriend Lennard en hond Ramses.