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Between desire and fear: a qualitative interview study exploring the perspectives of carriers of a genetic condition on human genome editing

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Human genome editing technologies are advancing at a rapid pace, and their potential disruptive implications lead to ethical and societal questions that cannot be addressed by scientists alone. Further consideration of different stakeholders' views on human genome editing is crucial to translate society's needs and values into thoughtful regulations and policies. We therefore explored the views of carriers of autosomal dominant disorders on somatic and heritable genome editing (SGE and HGE) and the role of their (secular or religious) worldviews. This group of stakeholders would be most impacted by the eventual clinical application of genome editing technologies and therefore their views must be taken into account. Ten in-depth semi-structured interviews were conducted, and data were analysed using reflexive thematic analysis. We found an overarching theme: 'Balancing between the desire to prevent serious diseases in individuals through HGE, and the fear of the harmful impact on society and nature' and three main themes: 'The benefits of SGE and HGE for individuals', 'the societal consequences of using HGE', and 'the consequences of interfering with nature through HGE'. Although the lived experiences of the participants varied, they were positive towards the safe use of SGE regardless of the severity of conditions, and most participants were positive towards the use of HGE but only to prevent severe genetic conditions. A few participants were against using HGE in any case, regardless of the severity of a condition, based on their religious beliefs. However, most participants with either religious or secular worldviews reported similar views on HGE, both regarding their desire to prevent serious genetic disorders and their fear of the impact on society and nature if HGE were implemented more widely. Reflecting on HGE involved complex and often ambivalent views. When engaging different stakeholders, space is needed for ambivalence and the weighing of values.

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Introduction

Disruptive genome editing technologies, such as CRISPR-Cas9, are developing at a rapid pace and lead to ethical and societal questions which cannot be answered by considering only pragmatic arguments such as safety and efficacy (Almeida and Ranisch, 2022; Coller, 2019; Kleiderman and Ogbogu, 2019; Smith et al., 2012). Many ethical concerns arising from values and social, cultural and religious beliefs cannot be addressed by scientists alone, especially when it comes to heritable genome editing (HGE) (WHO, 2021). HGE involves initiating a pregnancy with a modified embryo or gamete and thus passing on altered genes to a future child and subsequent generations (Baylis et al., 2020). A substantial majority of countries, including the Netherlands, currently prohibit HGE (Baylis et al., 2020; Overheid.nl, 2022).

However, scientific research involving germline genome editing (GGE) is permitted in the Netherlands if no pregnancy is induced and the embryos were not created specifically for research purposes but left over after fertility treatment (Overheid.nl, 2022). Globally, studies using GGE on human embryos are already in progress (Ma et al., 2017; Zeng et al., 2018; Zhang et al., 2019).

A clear distinction needs to be made between HGE and somatic genome editing (SGE), a therapeutic application of CRISPR-Cas9 and similar techniques. SGE is considered less controversial because consent can be asked, and altered genetic traits are unlikely to be passed on to future generations (Cornel et al., 2019; Ormond et al., 2017). However, within the disability community, issues have been raised against this application as well (Hoffman-Andrews et al., 2019). Therefore, an urgent global call for broad public engagement about the acceptability of human genome editing technologies has been made (Almeida and Ranisch, 2022; Andorno et al., 2020; EGE, 2021; Howard et al., 2018; Scheufele et al., 2021). For this public engagement to be effective, the value-laden perspectives of those affected by these technologies need to be explored, for example, when it comes to human nature and discrimination against people with genetic conditions or disabilities (Almeida and Ranisch, 2022; EGE, 2021; Scheufele et al., 2021; WHO, 2021). Despite the many position papers and recommendations on the subject, serious efforts to engage the public and stakeholders on the acceptability and use of human genome editing and the best way to do so are still being sought worldwide (Almeida and Ranisch, 2022; Iltis et al., 2021; Scheufele et al., 2021).

An important group of stakeholders, with respect to the future implementation of HGE, are carriers of an autosomal dominant genetic disorder (Kleiderman and Stedman, 2020). These are individuals who are already affected or have a significant chance of becoming affected and for whom there is a 50% chance of transmitting their genetic variant to their offspring. It is precisely these carriers who will be most impacted by the eventual clinical application of gene editing technology and therefore it is vital that their views are taken into account (Kleiderman and Stedman, 2020). Previous general public consultations, such as the Dutch DNA dialogue, show that just over two-thirds of respondents are in favour of using HGE to prevent serious heritable diseases and improve the quality of life of those directly affected, but only under strict conditions (Hendriks et al., 2018; Houtman et al., 2022). The few studies on the perspective of people with a genetic condition on human genome editing show that they may have different concerns regarding the acceptability of HGE, for example, because they perceive their condition as a positive source for their identity (Hoffman-Andrews et al., 2019; van Dijke et al., 2021). Moreover, previous research has shown that it is difficult for non-affected people, even for experienced genetic professionals, to assess the "seriousness" of a particular condition, often underestimating the quality of life of those affected (Crocker et al., 2015; Wertz and Knoppers, 2002). Yet the seriousness of a disease, from a general perspective, is often the prerequisite for access to certain technologies (Boardman and Clark, 2022).

In line with Almeida and Ranisch's (2022) conclusion that further consideration of different stakeholders' views on human genome editing is crucial to translate society's needs and values into thoughtful regulations and policies, this qualitative interview study aims to contribute to the global dialogue on the acceptability of human genome editing (Almeida and Ranisch, 2022). We explored the views of carriers of a genetic disorder on the different applications of human genome editing (somatic and heritable), paying special attention to the role of worldviews because human genome editing deeply touches on moral and spiritual considerations (Almeida and Ranisch, 2022). We have chosen the broad term "worldviews", which can be defined as the human ability to reflect on existential questions looking beyond religion and including secular (non-religious) frameworks for meaning-making (Josephson and Peteet, 2007; Taves, 2018).

Methods

We performed a retrospective interview study between April and June 2019 among 10 Dutch carriers of an inherited autosomal dominant disorder regarding their views on human genome editing and the potential role of their (secular or religious) worldviews.

Data collection and participants. By using convenience and snowball sampling methods, we recruited participants through the researchers' network, the patient alliance for rare and genetic diseases in the Netherlands (VSOP), the patient association for Huntington's disease, the patient association for hereditary heart disease, and through a Facebook group for BRCA1/2 mutation carriers. To be included, participants had to be of reproductive age and carriers of an autosomal dominant disorder. This means that they themselves are affected or have a (high) chance of becoming affected in the future and a 50% chance of passing on their carrier status to their (potential) children. Five parents of a child with a severe recessive genetic disorder asked by mail to be included in the study but did not meet our inclusion criteria. We suggested that they could contribute to the DNA dialogue that was taking place in the Netherlands at that time.

Procedure. The prospective participants first received an email with information about the study (Supplementary Information S1). Later, they were given more information by telephone and asked whether they wanted to participate. A few days before the interview, participants received an email with a link to a documentary with background information on human genome editing to ensure a basic understanding of CRISPR-Cas9 as a new technology (https://schooltv.nl/video/de-kennis-van-nu-in-de-klas-gentechnologie/). Nine out of ten participants watched the documentary before the interview. A total of 10 interviews were conducted. All interviews were conducted face-to-face, in Dutch, and lasted between 50 and 80 min. All interviews, except one, were conducted at the participants' homes. The interviewer had no personal prior knowledge of the participants. After obtaining written consent from the participants, the interviews were recorded and transcribed verbatim. As member check, all participants were offered insight into the transcript; seven participants used this option. In one case, this led to a minor correction. Participants were informed that interview transcripts would be kept for 5 years after the last publication and that audio recordings would be destroyed after they were transcribed. After

Table 1 Interview guide.

Topic	Question
Carrier status	You are a carrier of a hereditary disease. Would you like to tell me more about it?
Worldview	Can you tell me something about your worldview? This can be either secular or religious.
Applications of human genome editing	How do you view somatic genome editing for the treatment of your own condition?
	How do you feel about heritable genome editing given your worldview?
	How do you view the 'creation' of human embryos specifically for research?
	How do you feel about the idea of enhancing human embryos through heritable genome editing?
Genetic identity	To what extent is your identity determined by your condition?
Future developments	How will human genome editing affect the future?

Table 2 Example of the coding procedure.

Text fragment	Coding	Category	Theme
"But everything starts with a pretty story. The approach is 'we are going to eliminate sickness worldwide'. A great ambition! World peace for everyone! Let's do it! Yes, but if you look at history, there are plenty of people who have invented something that also has a very negative side."	It seems so good in the beginning, but history teaches us that there is a chance it will not end well eventually.	Negative consequences of new technologies	The societal consequences of using HGE

transcription, the interviews were analysed using MAXQDA software (version 2020).

Instruments. We constructed a semi-structured interview guide based on the literature published by the Beginning of Life Group from Amsterdam UMC, location Vrije Universiteit Amsterdam (Goekoop et al., 2020; Smalbrugge and Cornel, 2020; Van Dijke et al., 2018; Van Dijke et al., 2019), consisting of five topics: carrier status, worldview, different applications of human genome editing (e.g., SGE in patients or HGE to 'prevent' hereditary diseases or to enhance humans—improving human capacity when there is no pathology to be treated (Clarke et al., 2016)), genetic identity and future developments (Table 1; See Supplementary Information S2 for the extended interview guide). The Beginning of Life Group is a multidisciplinary research project focusing on emerging genetic technologies initiated in 2017 by the section Community Genetics of the Department of Human Genetics, the Department of Ethics, Law & Medical Humanities of Amsterdam UMC, and the Department of Midwifery Science of Amsterdam UMC, together with the faculty of Religion and Theology of the Vrije Universiteit Amsterdam. The interview guide was designed to allow participants to tell their own stories using a series of open-ended questions to capture a broad range of thoughts, feelings and value-laden perspectives of this stakeholder group on different applications of human genome editing.

Data analysis. We used reflexive thematic analysis (Braun and Clarke, 2006, 2019), coding and analysing the transcript as described: (1) becoming familiar with the data, (2) generating initial codes, (3) searching for categories, (4) reviewing the themes, (5) defining and naming the themes, and (6) writing the report. Two researchers independently coded text fragments of the first five interviews to reach inter-subjectivity of the results. From these codes, various categories were extracted to identify the important themes and subthemes in the interviews. The analysis was seen as a recursive process, and notes were taken throughout. The themes were selected according to their apparent importance in connection with the research questions. An example of the coding procedure is shown in Table 2.

Table 3 Background characteristics of the participants.

	Participants ($N = 10$)
Age-group	
20–29	1
30–39	3
40–49	5
50–59	1
Gender	
Male	3
Female	7
Genetic condition	
Huntington's disease	1
BRCA 1/2	3
Lynch Syndrome	2
CHEK2 breast cancer	1
Myotonic Dystrophy Type 1	1
Ehlers-Danlos Syndrome	1
Noonan Syndrome	1
Worldview	
Protestant	4
Roman-Catholic	1
Non-specific	5
Family status	
Children	5
No children	5
Educational level	
Vocational education	4
Higher vocational education	6

Results

A total of 13 participants initially agreed to participate in this study; however, three people could not participate because of family-related issues. All participants were of Western European ancestry. The background characteristics of the participants are presented in Table 3. It is important to note that autosomal dominant disorders may vary in their health burden, disruption and stigmatisation and that they present different challenges (Petersen, 2006).

Our study explored in-depth how carriers of an autosomal dominant genetic condition feel and think about somatic and

Table 4 Overarching theme, main themes and subthemes.

Balancing between the desire to prevent serious diseases in individuals through HGE, and the fear of the harmful impact on society and nature	
Main themes	**Subthemes**
• The benefits of SGE and HGE for **individuals**	• If it is safe, use it! (SGE) • The requirements for a serious condition (HGE) • Healthy children, happy parents (HGE) • The context-dependent value of an embryo (HGE)
• The **societal** consequences of using HGE	• Being human means being imperfect (HGE) • Fear of human misuse (HGE)
• The consequences of interfering with **nature** through HGE	• The appropriate role of humans in nature (HGE) • Identity (HGE) • Ecological consequences (HGE)

heritable genome editing (SGE and HGE) and how their worldviews affect their views. Although participants' experiences were diverse and shaped by various factors such as the nature of their condition, their coping style and the social implications they experienced, one overarching theme, three main themes and several corresponding subthemes were identified. The overarching theme was: 'Balancing between the desire to prevent serious diseases in individuals through HGE, and the fear of the harmful impact on society and nature'. The three main themes were: 'The benefits of SGE and HGE for individuals' (Theme 1), 'The societal consequences of using HGE' (Theme 2) and 'The consequences of interfering with nature through HGE' (Theme 3). These three themes and their subthemes are presented in Table 4 and are discussed and illustrated below with quotes translated from Dutch into English by a professional translator.

Overarching theme: balancing between the desire to prevent serious diseases in individuals through HGE, and the fear of the harmful impact on society and nature. Most participants shared the desire to prevent serious genetic conditions through HGE as long as it can be applied medically and safely to individuals and their families. However, once HGE would also be more widely used for mild(er) conditions or human enhancement, participants were no longer in favour of using HGE, as several negative consequences were feared. These include an increase in discrimination, a shift away from what is considered 'normal' and a decrease in tolerance for what deviates from society's ideals. Furthermore, several participants indicated that the use of HGE could disrupt the course of nature, with potentially unforeseen consequences.

Theme 1: The benefits of SGE and HGE for individuals. Many participants mentioned their desire to increase the physical and psychological well-being of individuals and their immediate families through human genome editing technologies. Regarding the acceptability of using somatic genome editing (SGE), participants only referred to pragmatic arguments such as medical safety and effectiveness. With regard to the use of HGE, however, besides safety as an obvious prerequisite, the seriousness of the condition, in particular, was very decisive for the participants. The prevention of a serious condition was considered such an important value that other values important to some participants, such as the protectability of an early embryo, were sometimes given less weight in that respect.

If it is safe, use it!. The most important question for all participants when considering SGE was: 'Is the procedure medically safe?' If technically possible and proven safe, most participants would see SGE as a 'normal' medical intervention and would like to apply the procedure to themselves or their already-born children to make them physically healthier and improve their quality of life. As P8 explained: *"All medicines are not passed on in the germline. […] For me, then, it just becomes a medicine and if it is approved by the EMA or the FDA or whatever, then I would say: go for it!"* The severity of the condition did not play a role in this for the participants. One participant did explicitly specify that SGE should not be used for improvement beyond 'normal' but only to cure diseases. Many participants considered it an advantage that the effects of this application are supposed to be limited to the person to whom the procedure is applied and do not affect offspring or identity.

The requirements for a serious condition. Regarding the use of HGE, many participants said this should only be allowed in the case of a severe genetic disorder, specifying the following criteria: a high probability of occurring, 80 or 100% instead of 5%, being life-threatening, no alternative treatments, such as surgery or medication available, an enormous impact on the quality of life and a large effect on family relationships. As P10 said: "*You must limit it very much to those conditions for which there are really no alternatives.*" Most participants found it difficult to indicate where to draw a general line between serious and less serious conditions, recognising that personal factors, such as what a person can endure or has learned to live with, play an important role: *"Well, if you are really affected […] with MS or a disease that really limits you, then I can understand that people want to be helped, if that improves their quality of life, but […] how far do you go? […] For some people it is…well, they don't feel limited at all and for others it is like; yes, it does limit me very much."* (P6).

Although many participants identified more or less the same strict requirements that a serious condition must meet, they provided very different examples of conditions that, in their opinion, do *not fit* within these requirements: several mentioned HIV, some hereditary diabetes, hearing or vision problems. Another mentioned cancer, muscle diseases and heart defects as not suitable to use HGE for. As a way to illustrate a truly mild condition, some mentioned acne or sweaty feet. Huntington's disease, multiple sclerosis (MS), hereditary breast and ovarian cancer (BRCA), cystic fibrosis (CF), Down syndrome, dementia and amyotrophic lateral sclerosis (ALS) were mentioned as examples of serious conditions. Almost all participants were convinced of the importance of distinguishing between serious and less serious conditions. Because with the blurring of that boundary, HGE could be applied much more broadly, leading to other, possibly even bigger problems by compromising important societal values, such as tolerance, equality, or disrupting the course of nature.

Healthy children, happy parents. Several participants indicated that, in case of a serious condition, parents have the right to modify the DNA of their own future child: *"It's their child […] the child can't make a decision yet, so yes then the parents are ultimately the ones who make a decision on that (HGE)."* (P4). Many participants mentioned a better quality of life, healthier children and happier parents and less (relationship) stress as important benefits of HGE for carriers of a genetic condition and their offspring *"Then later on, when it's a girl, my child won't have to go through the checks I have to go through now and she won't have the stress that comes with it."* (P5). Another participant explained that he and his partner were on a trajectory for embryo selection in order to have a child without his condition: *"After me it will end […]it is tough to have that disease, but you can still have a very good life, but I don't want to pass that on to the next generation."* (P8). He added that if HGE would be allowed and would safely lead to more viable embryos, he might have preferred HGE to embryo selection to ease the burden of many IVF rounds for his partner. In contrast, two participants declared that they struggled with the potential use of HGE anyway, regardless of the severity of the condition. They both believed it was against God's will, but also saw that this technique could potentially alleviate human suffering and struggled with this dilemma: "*But, if it (the use of HGE) really is against your principles […] you have an even bigger problem […] It is better to be physically ill than to be spiritually troubled."* (P1), and P3: *"I think it is God's principle that the DNA of mummy and daddy come together and then something new is created. I don't want to interfere with that at all […] The consequence that I will pass on my disease, yes, that is part of it."*

Participant 3 added that it becomes much more difficult to adhere strictly to your own principles as the severity of the condition increases: *"With my hereditary disease, that's pretty easy to say because I know: we always detect it in time, the chance that it will kill me is pretty small, but of course that's different if you have ALS or something."*

Some other participants, who also had a religious worldview, recognised the potential dilemma between their belief that God is opposed to HGE and the relief of human suffering through HGE, as described above, but made a different assessment because they considered this technique a gift from God: *"From a biblical perspective, people often say […]that these (technologies like HGE) are not allowed, but I think that this is also short-sighted […]I believe that they (researchers and medical doctors) have also received that knowledge from God […] and that is not something that God could be against, I think."* (P2).

The context-dependent value of an embryo. Questions about the acceptability of HGE also relate to the value and status of embryos. To investigate whether the technique is safe and effective, research on embryos created specifically for research would be needed. Two participants with a religious worldview, the same ones who were against HGE in any case, felt that an embryo should not be touched in any situation because of their intrinsic worthiness: "*To just put twelve babies in the freezer and then throw them away. That has really to do with my religious beliefs. If I didn't have religious beliefs, I would think: 'oh, it has no soul, get rid of it'."* (P1). Although there were significant differences in how the other participants thought about an embryo, ranging from a clump of cells to a person from the moment of conception, they all indicated that they felt it was necessary to create embryos for HGE research to increase the safety of the technology. When weighing up values and interests, the value of safely preventing serious genetic conditions was apparently considered more pressing by several participants than the protectability of embryos. This applies even in those cases where the participant, in principle, regards an embryo as a person from conception onwards, as all participants with a religious worldview did, like P2: "*I am anti-abortion, with the odd exception here and there […] of course, it does not tally with research on embryos if you put it like that. On the other hand, if you think it (the use of HGE for serious diseases) is a good thing, you also want these kinds of developments to be tested."* P7, who also has a religious worldview, shared the same considerations: *"From the moment of conception, it is life, and it is not for me to be the judge of life or death." "But if you don't do those tests (research on created embryos), you can't apply it (HGE). If this is the solution that will stop all the diseases, I think it's okay. Up to a certain point of course, I don't think you should keep doing that for years."* A religious worldview is apparently not necessarily the determining factor in how participants think about the creation of embryos for HGE research.

In other respects, for participants both with and without a religious worldview, the value of the embryo also seemed to depend on the purpose for which it was created, either to establish a pregnancy or for research purposes. Participant 10 first reflected on how she felt about embryos created for research purposes: *"To me that (an embryo) is really just a clump of cells, just like they make mini-intestines and stuff now, but to me that's really just cell division but not a baby yet."* Later during the interview, she mentioned the surplus embryos of her friends that were the result of an IVF procedure and the difficulty of deciding what to do with them because they were part of a fertility trajectory: "*The other couple I know, still have embryos (left over after IVF) and they are also wondering what to do with them. Because somehow, they are little children and especially because you've struggled so much with this desire to have children."* Another participant showed the same deliberations. On the one hand, she favoured the use of embryos for research in a general sense, but reflecting on her own failed IVF attempts, she said: *"I hope I did not consent to research (on her surplus embryos) then, because I probably do think […] maybe it has something of a soul after all."* (P4).

Theme 2: The societal consequences of using HGE. Besides the potentially positive impact of using HGE for serious conditions on individuals and their families, several participants also saw threats to societal values they hold dear, such as less tolerance towards people who deviate from the 'norm'. The broader the potential deployment of HGE, with milder conditions or for enhancement, the more concerns arose among participants, for example, that HGE might be used in the pursuit of more human perfection or for more power.

Being human means being imperfect. All participants expressed concern that HGE may be used as a tool in today's increasing societal striving for perfection. Many wondered what perfecting future children might mean for society in terms of tolerance, solidarity, human equality and what it would mean for how we want to be 'human'. Some participants reflected in this regard on how HGE, if used for 'perfection' could affect the parent-child relationship: "*I think genetic editing to be stronger or prettier or smarter, would actually imply that you are not good the way you are and that is exactly what I am so consciously working on with the children, that despite all your faults, you are OK*." (P10). Participant 2 also mentioned possible negative consequences if parents were able to alter the DNA of their unborn child to make it smarter: "*If you can adjust intelligence, so to speak, you really assume that […] it will be really easy at school, but there are so many other factors that also influence where your child will eventually end up. And then parents are also pretty much deceived*

[…] in the parent-child relationship, that has an influence, that relationship will not improve."

Almost all respondents mentioned the current (negative) influence of social media, such as Instagram, on the existing body image and on the idea that life is makeable: "*You can already see it in social media […] everyone pretends to have such a great life and it only becomes more so. The pretence of appearance and perfectionism is becoming more and more prominent and where does it stop in the end?"* (P4). Several participants were afraid that the intolerance for people who deviate from the 'norm' will increase: *"I think maybe an even bigger chance of discrimination […] suppose you do have this disease, that people say: why didn't your parents do something?"* (P1), or P9: *"I'm actually afraid of this manufacturable human being, of creating a world in which everyone is just the same, so that there is even less room, I think, for people who are different."*

A number of participants said they were worried that if every disease or disability were ruled out, people would no longer be able to accept that life is sometimes difficult and deal with it. Some shared examples from their own lives, sometimes also advising (fictitious) others to accept life, their children, and themselves despite possible limitations, as they have learned to do as well, like P9: "*At a certain point you must accept that you have certain limitations. No matter how difficult it is […] If I can't buy a Ferrari, I'm not going to buy a Ferrari, to put it bluntly."* Other participants also shared how they were coping with their conditions, often emphasising that their condition was 'manageable' despite the severity: *"OK, this is very unpleasant but luckily we have a good healthcare system in the Netherlands and you can do all sorts of things to ensure that your life is still good."* (P8), or P7: *"I have pain somewhere every day. I have accepted it. Because if I don't accept it, you don't have a life anymore."*

Although none of the participants, regardless of their worldview, saw suffering as inherently positive or God-intended, several said that dealing with suffering can also bring meaning. For example, some participants mentioned that people could grow stronger from difficulties, learn to cope with obstacles and become 'better' persons as long as they do not succumb to them. As P10 explained: "*You don't choose it, but 'every downside has its upside', and it's also a gift, that you are pulled back hard, and told to take a good look at what you are doing with your life."*

Fear of human misuse. Some participants were afraid that HGE might be abused by influential individuals, commercial parties or a faulty regime, even more so if the intention is to enhance human beings: "*Suppose people who have money can do it and people who don't have money can't do it, very deep divisions will arise."* (P4). A few mentioned that something might start out well and be used for good but end up being used for worse under the influence of money or power and might lead to superhumans or super armies: *"That is where my concern very much lies, that we may want that (HGE), but that in 10 or 15 years […] we haven't been able to see the consequences. What superhumans we have been able to create and that there is someone in […] some police or weird state […] who is delusional and thinks: 'I'm just going to sort that out my own way'."* (P3). Several participants also referred to past examples, such as the Second World War and the highly charged history of eugenics: *"Personally, I find that (human enhancement) very scary […] it's a bit like the Übermensch idea from the Second World War."* (P8).

Theme 3: The consequences of interfering with nature through HGE. A number of participants also expressed concerns regarding the consequences of interfering with nature or the natural order through HGE. They spoke about how humans should exercise caution towards intervening in nature and how they saw identity in relation to their genetic condition. In addition, they reflected on the possible consequences of HGE on planet Earth in terms of ecological impact.

The appropriate role of humans in nature. Several participants indicated that they had questions about the role human beings should play when it comes to interfering with nature. Participants, both with and without a religious worldview, expressed great respect for the delicately balanced systems in nature, regardless of whether this is seen as divine or natural providence. Especially when it comes to human enhancement, participants felt that an area was entered that is off-limits to humans. Several participants, regardless of their worldviews, searched for words to adequately express these concerns, sometimes using 'religious' language such as referring to the awareness of certain limits to the role of humans in the natural order or regarding the beginning of life as a miracle: *"This sounds almost religious when I say it like this, but I wonder if it is always up to us to decide what is necessary to improve. […] I don't think there is a higher being that makes those decisions for us but the fact that you can do something as a human being doesn't mean that you must do it. I find it difficult, it's a very personal feeling in the end."* (P8). Similarly, P4 reflected on the difficulty in defining the feeling of reverence evoked by nature whereby a sense of unease arises when humans interfere with it: "*It is still something miraculous that from an egg cell and a sperm cell a child is born and I think that we have already come this far to possibly be able to prevent the diseases or put a stop to them, of course that is very positive […] but it doesn't give me a good feeling, I find it a bit difficult to describe but it just doesn't feel right. You also have to let nature take its course so to speak*."

Identity. This sense of reverence for 'how things are meant to be' also played a role for some participants on the subject of (genetic) identity. Several felt it was important to remain who you essentially are and that identity should not be changed by editing the human genome, which, incidentally, most participants doubted was possible. One participant, however, worried in this regard whether people would still feel part of their family when modified: *"Your identity also comes from your parents and generations (before) and of course you inherit your DNA but if you start cutting a lot then you also change the whole DNA structure and then, in my opinion, not so much of your self remains."* (P6).

Participants differed in the extent to which they felt that their identity coincided with their condition. Several participants did not experience their condition as a fundamental part of their identity, although it had shaped them like P7 said: "*This disease is part of me, I am not this disease.*'" or P10: *"I am more than my DNA … it's not who I am."* One participant felt that part of her identity was hidden because of her condition: *"Of course I am just who I am inside me. I just can't express who I am. So you don't see how creative I am, how active I actually am in my head […] if I have to go out for a day I drive a wheelchair, while in my head I'm hopping.*" (P1). Another participant felt that her identity was in a way largely defined by her condition and that this was reinforced by her active involvement with the patients' association: *"At one point I was sort of my disease, but also because I was very involved with the patients' association […]it (my condition) is not my whole identity, but if I look at certain behavioural things, that's determined by [name of condition] that's just part of my life, I can't see that separately […] As I said, it's in my whole body, in my brain, my whole way of doing things."* (P9). Still, for this participant, the right to health (through HGE) outweighs the right to an unchanged genetic identity: *"I think happiness and health would outweigh that genetic identity for me. You cannot do anything with that genetic identity as such. You are who you are*

[…]And anyway whichever way you look at it, your cells are dividing, [DNA]changes are taking place." (P9).

Ecological consequences. A few participants, despite their sympathy for people's individual desire to be healthy or conceive a healthy child, also expressed a sense of responsibility towards planet Earth by which too much intervention in the natural order can lead to problems such as overpopulation or environmental stress: "*Looking purely at my personal motivation it's: 'yes, I would do it (HGE) because I want a healthy child', purely on a selfish basis, but then when you look at humanity, I think 'shouldn't we just let nature take its course', because we also have overpopulation and no one wants to be sick, but if everyone is healthy then the planet explodes*." (P10).

Discussion

This qualitative study aimed to explore the views of carriers of an autosomal dominant condition on somatic and heritable genome editing (SGE and HGE), paying special attention to the role of worldviews. We found an overarching theme: 'Balancing between the desire to prevent serious diseases in individuals through HGE, and the fear of the harmful impact on society and nature' and three main themes. The main themes were: 'The benefits of SGE and HGE for individuals, 'the societal consequences of using HGE', and 'the consequences of interfering with nature through HGE'. The study showed that although the lived experiences of the carriers varied, participants were positive towards the safe use of SGE regardless of the severity of a condition, and most participants were positive towards the use of HGE but only for the prevention of severe genetic conditions. Two participants were against the use of HGE in any case, regardless of the severity of a condition, based on certain religious beliefs, in which an embryo has a soul from conception and is therefore highly worthy of protection and in which great reluctance is felt to interfere with God's biological principles regarding the beginning of life. Surprisingly, other participants with a religious worldview made a different assessment and saw HGE as a gift from God or gave more weight to alleviating suffering using HGE, despite the high value they placed on an embryo. In addition, independent of whether participants held religious or non-religious worldviews, many similar feelings and thoughts about HGE were reported, both in terms of their desire to prevent serious genetic disorders in individuals and their fear of possible consequences if HGE were to be applied more widely. What was particularly remarkable here was that all participants, regardless of their worldview, were opposed to another worldview that they perceived in society in which the pursuit of perfection plays an increasingly important role and to which they feared HGE might also be used as a tool.

The participants in our study regarded somatic genome editing (SGE) as an ordinary medical procedure to which they had little objection as long as the technique was medically safe and effective. This is in line with previous studies among the general public and professionals who had fewer objections to SGE than to HGE (Hendriks et al., 2018; Van Dijke et al., 2018; van Dijke et al., 2021). However, in a previous study among couples at high risk of conceiving a child with a genetic disorder, SGE was seen as less preferable than HGE. These couples indicated that they would rather undergo preimplantation genetic testing (PGT) or HGE themselves than put the burden of treatment on their child using SGE (van Dijke et al., 2021). This may be explained by the fact that the high-risk couples were asked to make comparisons between different reproductive techniques and, unlike the participants in our study, were all actively considering PGT. Moreover, the participants in our study may have been less informed about the potential burden of SGE treatments, such as painful medical procedures or lengthy hospitalisation, which may have made them more positive about it. This underlines the importance of offering sufficient factual information about the technology for participants to make a balanced consideration about different applications of genome editing. Another contrast with an earlier study on people with hereditary retinal diseases, the participants in our study did not fear an increase in negative attitudes towards their condition or people with their condition when using SGE (Hoffman-Andrews et al., 2019). A possible explanation for this may be the types of genetic conditions that were included in our study, mostly late-onset (chronic) conditions that involved physical suffering and were not always clearly visible. It has been argued that especially early onset conditions can be a potentially positive part of both personal and communal identity, which influences people's views on their own condition and, therefore, on genetic editing technologies (Boardman and Hale, 2018; Hoffman-Andrews et al., 2019). These results emphasise the importance of including a wide variety of patient groups with different types of genetic conditions and the need for both medical and social lenses in assessing the acceptability of HGE (Kleiderman et al., 2022; Kleiderman et al., 2020).

As for HGE, if used for individuals and their relatives with severe genetic disorders, most participants would support it. However, as soon as HGE would be used more broadly for less severe disorders or enhancement purposes, participants were afraid that humanity, in a broader sense, would not benefit. By stretching the conditions for using human genome editing technologies, the consequences will be different: HGE will cause less harm if only a small group would use it to prevent their own serious condition, compared to when large groups would want to bring the healthiest possible children into the world through HGE (Morrison and de Saille, 2019; Padela and Aparicio, 2019). Therefore, participants stressed the need to make a clear distinction between serious and less serious conditions. At the same time, participants expressed how difficult it is to draw a general line because, in addition to the type and expression of a certain condition, contextual factors such as people's coping ability influence the assessment of what qualifies as a serious condition (Boardman and Clark, 2022; Kleiderman et al., 2022; Petersen, 2006; Wertz and Knoppers, 2002). Besides these contextual factors related to individuals and their personal experiences, there are also country-specific contextual factors related to equal access to or quality of healthcare that influence participants' responses and make it difficult to generalise them. For example, in a South African deliberative public engagement study on heritable genome editing, most participants indicated that they would find the use of HGE for immunity against HIV desirable because of the high threat of the HIV epidemic to future generations and the huge economic costs involved (Thaldar et al., 2022). In contrast, in our Dutch study, HIV was mentioned several times as a disease for which HGE should not be used, as participants mentioned the availability of good treatment options and opportunities to prevent the spread of HIV. The interviews revealed that participants made value trade-offs regarding the acceptability of HGE. On the one hand, if HGE were to be used for a relatively small group of people with severe conditions, values such as the alleviation of suffering, promotion of health, quality of life and autonomy of the future child/parents were given great weight. However, if HGE were to be used much more widely, for less severe conditions and enhancement purposes, participants feared that it would compromise other important values, such as solidarity, equality, tolerance, diversity, unconditional acceptance of offspring, acceptance of life as is, reverence for nature and humility. Although the participants had different worldviews, they were quite united in their rejection of a worldview they perceived in society where the manufacturability of life plays a major role.

Participants were concerned about this development and questioned how HGE would affect norms in our society around 'normal' functioning and health and how this might influence people's freedom not to opt for HGE and the right to existence with disabilities (Almeida and Ranisch, 2022). Participants instead emphasised more acceptance of life as is and tolerance for what deviates from what society sees as ideal. They also made a case for a more modest human role in the natural order, allowing nature to take its course because the consequences of too much intervention could be greater than anticipated. Participants struggled to put words to their feelings of unease. Adequate language seems to be lacking for challenges posed by what has been termed 'postnormal' scientific developments that are highly complex and have major societal implications, such as HGE (Scheufele et al., 2021). The literature shows that references to nature and (un)naturalness are used as a way to express emotions and underlying moral concerns related to the question of how to deal with the newly acquired ability to influence human DNA through human genome editing in ways never before possible in human history (COGEM, 2022; Morrison and de Saille, 2019). We should be careful not to dismiss these feelings too quickly as related to a lack of scientific knowledge, also known as the 'deficit model' of public understanding of science (Morrison and de Saille, 2019). Instead, it requires clarification of people's underlying values and cultural, social and religious beliefs towards HGE, as also recommended by WHO (WHO, 2021).

To ensure the safety of HGE, research on the safety and efficacy of the technique would be needed. This research requires embryos on which the technology can be tested. Scientific research involving germline genome editing (GGE) is permitted in the Netherlands if no pregnancy is induced and the embryos were not created specifically for research purposes but 'surplus' after fertility treatment (Overheid.nl, 2022). Our findings showed that the relationship between how participants thought about the status of an embryo and their views on the use of embryos for HGE research is rather complex. Participants with a religious worldview in this study all considered an embryo to be a person from the moment of conception. Yet some participants with a religious worldview indicated that they supported using embryos for HGE research based on a weighing of values, namely the moral worth of an embryo versus the value of promoting the health of future children through the safe use of HGE. Furthermore, in line with the literature on the various ways embryos can be perceived, it appeared that the meaning that participants gave to embryos also depended on the intention and purpose for which the embryo was created and was thus subject to change (Goedeke et al., 2017). Some participants considered surplus embryos more morally valuable than embryos created for research purposes only. In the Netherlands, by contrast, surplus embryos may be used for research after parental consent, while creating embryos for research is prohibited (Overheid.nl, 2022).

Strengths and limitations. The strength of this study is that, to our knowledge, carriers of autosomal dominant disorders in the Netherlands have not been interviewed before about their views on human genome editing and the role of their worldview, where we were able to map a broad spectrum of in-depth views. As this is a small group of participants, the external validity of the results is limited and different answers may be expected in a different setting. Nevertheless, we believe that the achieved information power of our study appears strong because it involves a group of participants with specific characteristics having experiences and views that have not been described before (Malterud et al., 2016). The interviews were conducted by an experienced interviewer and were highly relevant to the research question adding new knowledge to the field. Moreover, the last two interviews did not add any new themes, which we considered a confirmation of sufficient sample size. For this study, participants mainly signed up themselves, which may have caused a bias in our carrier population. Carriers willing to participate in an interview study on human genome editing technologies may have different views than carriers who do not want to be interviewed. We interviewed native Dutch people for our exploratory interview study, although this does not reflect the diversity of the Dutch population. How Dutch people with a migration background and/or other (non-Christian) religious worldviews perceive human genome editing was not addressed in this study, which we see as an important recommendation for future research to which we would like to contribute ourselves by also giving a voice to groups that are usually underrepresented in public and stakeholder engagement (Houtman et al., 2023).

Conclusion

Our study reveals that reflecting on HGE evokes complex and often ambivalent thoughts and feelings. Carriers of an autosomal dominant condition are moving back and forth on a continuum between, on the one hand, their desire to reduce individual suffering through HGE and, on the other, their fear of the consequences if HGE is allowed and becomes more widely practised. When engaging broadly with the public and stakeholders, we recommend valuing and guaranteeing extensive space for ambivalence and deliberation. In addition, we recommend analysing the weighing of values that causes the observed ambivalence, in which the ambivalences are embraced and thematised rather than resolved.

Data availability

The datasets generated during and/or analysed during the current study are not publicly available due to data confidentiality and the Dutch language but are available from the corresponding author on reasonable request for researchers who meet the criteria for access to confidential data.

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Author contributions

All authors contributed substantially to the design, analysis and interpretation of the data of this study. WG prepared the draft manuscript and coordinated its finalisation. The other authors commented and gave feedback on the draft manuscript. All authors gave feedback and their final approval of the final version of the manuscript. All authors are accountable for all aspects of the work.

Competing interests

As of 1st September 2022, WG, CvE and MC are involved in a Netherlands Consortium, "Public Realm Entrance of Human Germline Gene Editing", funded by the Dutch Research Council (NWO) with project number [NWA.1389.20.075]. The other authors declare no competing interests.

Ethical approval

The Medical Ethics Committee of Amsterdam UMC location VUMC reviewed and waived this study as human subject research (Ref nr. 2019.177). This study was performed in line with the principles of the Declaration of Helsinki.

Informed consent

All participants received oral and written information about the purpose of the study prior to the interview. They were informed about confidentiality, the anonymity of any quotes, and the possibility of withdrawing at any time without giving a reason. Participants gave their oral and written informed consent for participation by signing an informed consent form.

Additional information

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