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

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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, such as intelligence). While experts have called for public engagement, it is unclear whether and how much 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 multinomial 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.

STUDY FUNDING/COMPETING INTEREST(S): Young Academy of the Royal Dutch Academy of Sciences (UPS/RB/745), Alliance Grant of the Amsterdam Reproduction and Development Research Institute (2017–170116) and National Institutes of Health Intramural Research Programme. No competing interests.

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Key words: gene editing / preimplantation diagnosis / bioethics / public opinion / surveys and questionnaires / germline genome editing / genetic enhancement / genetic disease, inborn / genetic techniques

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; Lander et al., 2019; Botkin, 2020). However, scientists expect that safety and effectiveness will improve, making clinical use of GGE feasible in the foreseeable future (Smith et al., 2012; NASEM, 2017). 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 (NASEM, 2017; Ormond et al., 2017; Howard et al., 2018; NCOB, 2018; Andorno et al., 2020).

Various influential bodies have concluded that clinical application of GGE may be acceptable under certain conditions (NASEM, 2017; Ormond et al., 2017; de Wert et al., 2018; NCOB, 2018). 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 (NASEM, 2017; Knoppers et al., 2018)), and contribute significantly to the future child's well-being (Smith et al., 2012; Knoppers et al., 2018). Notably, these conditions do not cover all ethical questions that GGE raises, including concerns about justice and eugenics (van Dijke et al., 2018; Andorno et al., 2020).

Many scholars have argued for public engagement (NASEM, 2017; de Wert et al., 2018; NCOB, 2018; McCaughey et al., 2019; Andorno et al., 2020). 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 (Srinivas, 2017; NCOB, 2018).

Several studies have since investigated public views. GGE acceptability varies considerably by case and between studies, ranging from 8% to 72% (Blendon et al., 2016; Funk and Hefferon, 2018; Delhove et al., 2020). 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 GGT's safety (Robillard et al., 2014; Wang et al., 2017), effectiveness (Kalfoglou et al., 2005), costs (Xiang et al., 2015; Wang et al., 2017) 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 (Scheufele *et al.*, 2017; McCaughey *et al.*, 2019)), 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: (i) 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); (ii) effect of preventing the index disease or introducing the desirable characteristic on the future child's well-being; (iii) risk that the reproductive technology would cause major abnormalities (e.g. though off-target effects); (iv) effectiveness (i.e. chance of a pregnancy that results in a live birth); (v) costs covered by national health insurance; and (vi) 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 iv), 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 vi) were framed as options leading to genetic parenthood (NASSEM, 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 judgement. 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, €10 000 or €20 000).

Survey design

The six treatment characteristics and their 2–3 levels resulted in 216 [$2^3 \times 3^3$] 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).

The survey introduction explained how GGE would work and current alternatives. Furthermore, the survey listed several ethical

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?

- Yes
 No (this should be prohibited)

Would you want to use gene editing on your embryo in this scenario?

- Yes
 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'.

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 (Singer et al., 1998; Gaskell et al., 2003, 2006).

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 [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 1857 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 (>10 000) 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 multinomial 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 multinomial 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 counterbalance 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, e.g. 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 towards 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 ethics 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 towards 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).

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

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

		Proportion (%)
Sociodemographic characteristics		
Male gender		576/1136 (50.7%)
Age (year)	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%)
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 towards science		
Engagement with biotechnology ^c (mean ± SD, maximum score is 1)		0.37 ± 0.28
Nature versus nurture beliefs	Heredity and genes determine the behaviour 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 behaviour of a person most	271/1136 (23.9%)
	Heredity and genes determine the behaviour 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%)
	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%)

(continued)

Table 1 Continued

		Proportion (%)
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%)

^aPersons were defined as having a non-western ethnic background if 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>).

^bParticipants were asked to place themselves on a 'political' scale of 0–10 (left-right and progressive-conservative), which were grouped into categories.

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

participants' choices. [Supplementary Fig. S1](#) displays the willingness to use GGE when an alternative treatment/procedure was available.

Associations with sociodemographic characteristics, attitudes towards 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 €13 950 lower, both cases would be equally acceptable (95% CI: €8400–19 500). 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.

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. Weisberg *et al.*, 2017; McCaughey *et al.*, 2019). 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 as 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

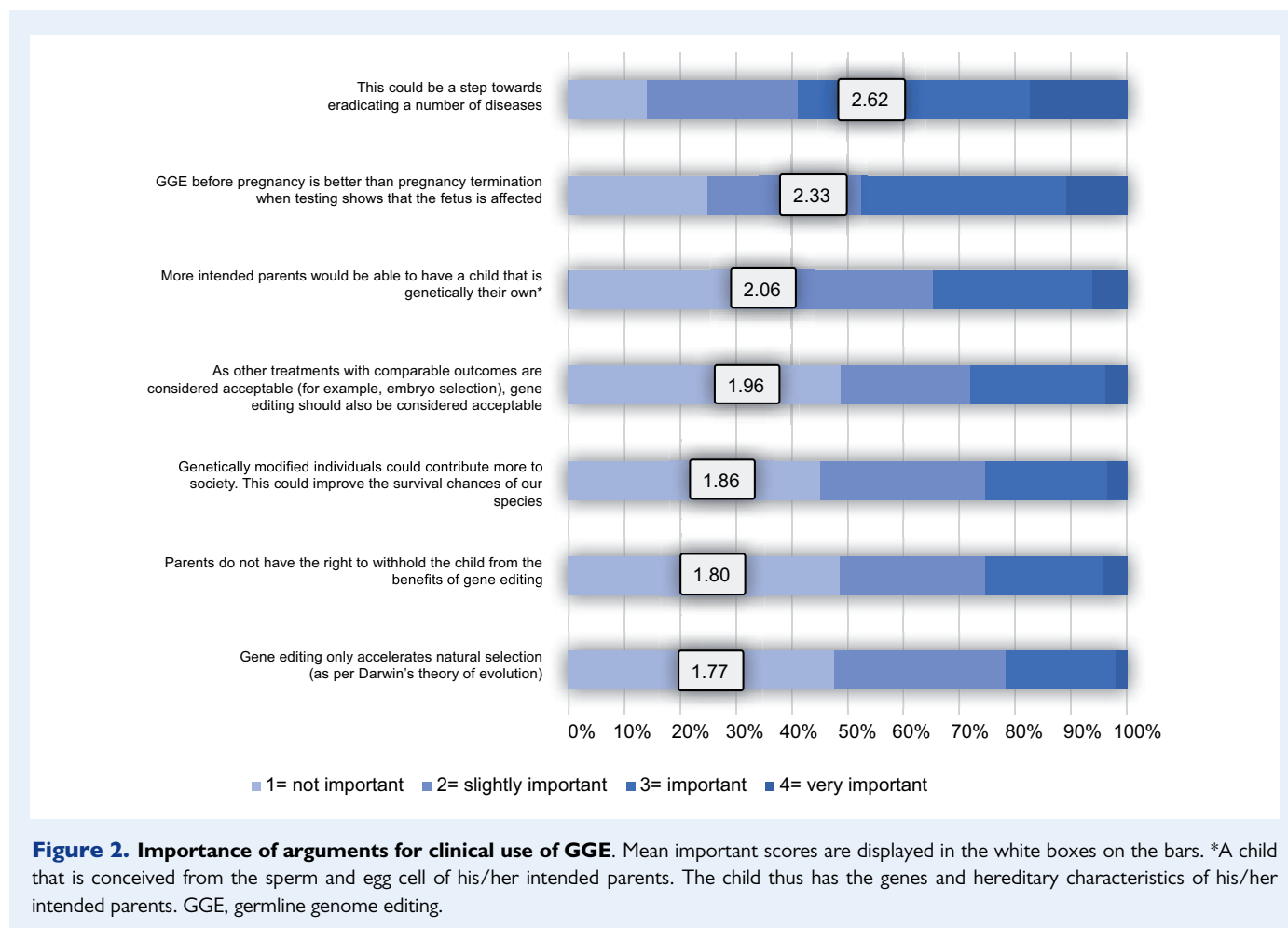


Figure 2. Importance of arguments for clinical use of GGE. Mean important scores are displayed in the white boxes on the bars. *A child that is conceived from the sperm and egg cell of his/her intended parents. The child thus has the genes and hereditary characteristics of his/her intended parents. GGE,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

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 paediatric 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

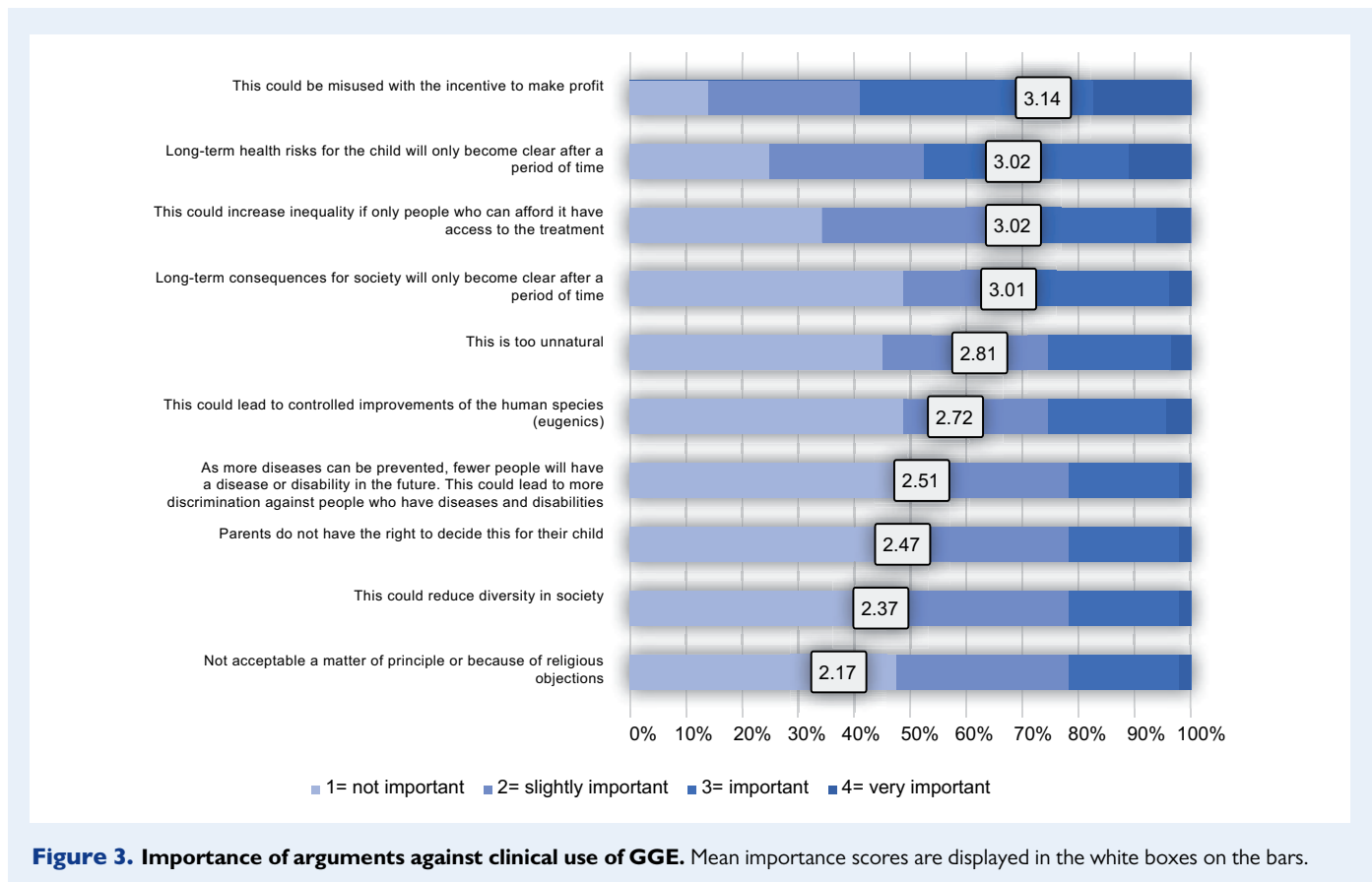


Figure 3. Importance of arguments against clinical use of GGE. Mean importance scores are displayed in the white boxes on the bars.

effectiveness was not clearly defined, making comparison difficult) (Lewis *et al.*, 1997; Kalfoglou *et al.*, 2005; Hendriks *et al.*, 2018). 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 ESHRE 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 centres (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 (Xiang *et al.*, 2015; Wang *et al.*, 2017). 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 (Wellcome Trust, 2005; Hui *et al.*, 2009). 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 disfavoured 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.

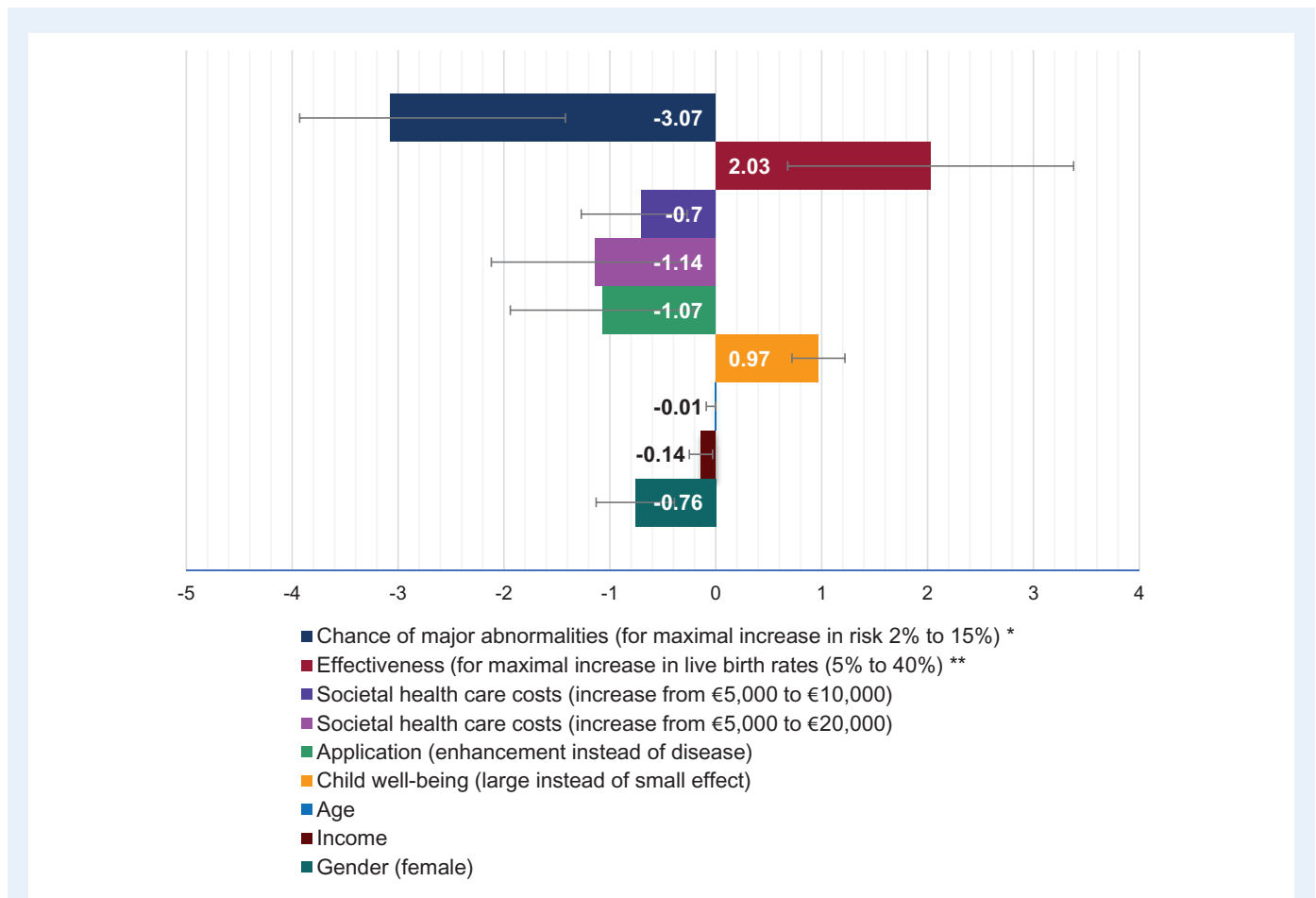


Figure 4. The effect of the treatment characteristics on whether participants thought GGE should be allowed in the Netherlands, when no alternative treatments/procedures are available. Model parameters: 2 log-likelihood = -542; Pseudo $R^2 = 0.591$; consistent Akaike Info Criterion = 1183. *A translation 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].

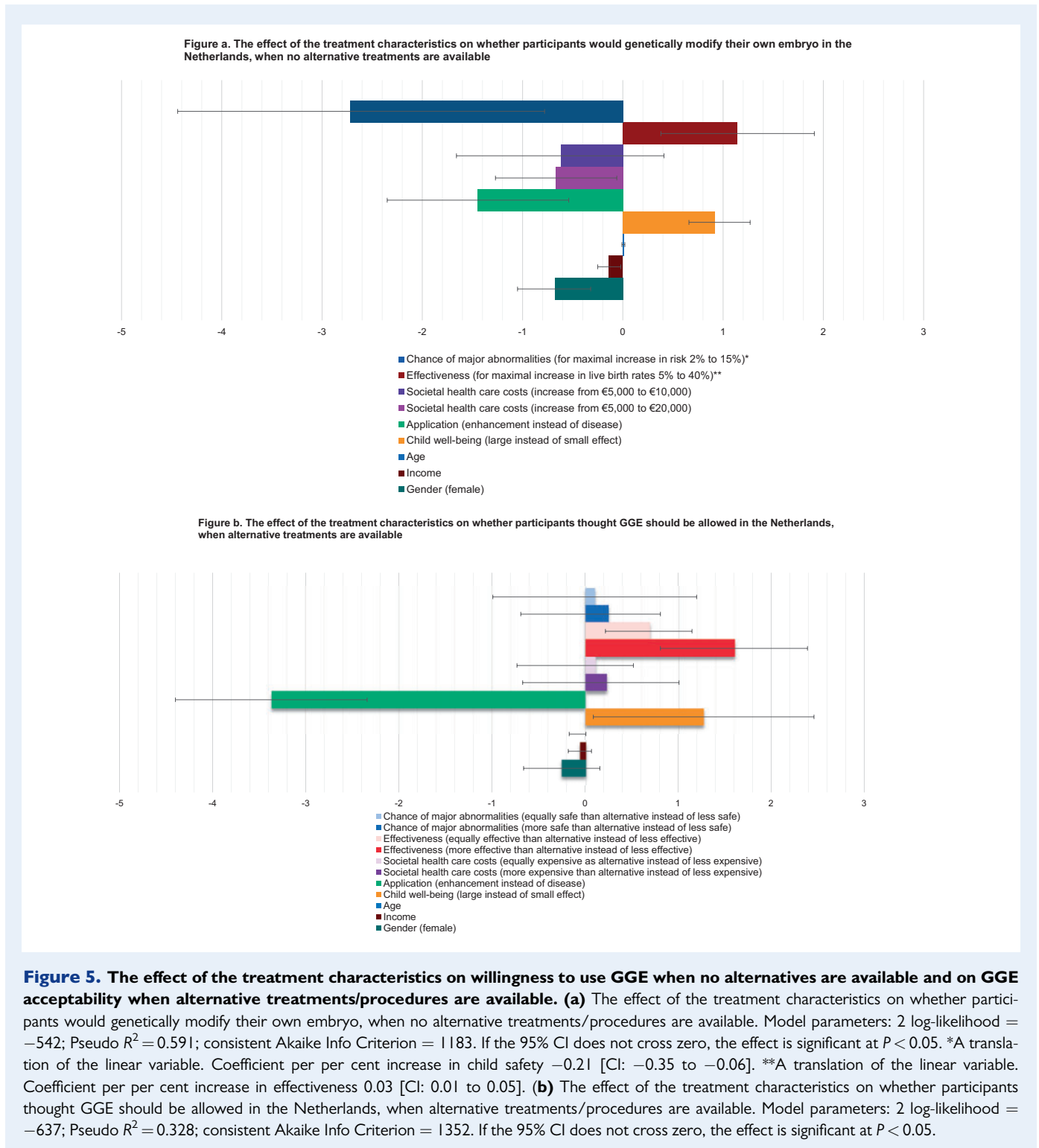
The effect of GGE on child well-being was previously reported to be a key argument for GGT (Robillard et al., 2014; Hendriks et al., 2018). Furthermore, previous studies compared the acceptability of using GGE to prevent different diseases (e.g. HIV or a neuromuscular disease (Hendriks et al., 2018)). 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. Wellcome Trust, 2005; Weisberg et al., 2017), other background variables had no effects in this study. This may relate to these previously reported effects being application- and context-dependent (Wellcome Trust, 2005; Scheufele et al., 2017).

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; Smith et al., 2012; NASEM, 2017; Ormond et al., 2017). 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. 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).

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

I.D. contributed to the data collection, analysis and manuscript drafting. M.W. contributed to the study design, analysis and manuscript drafting. B.E.B. contributed to critical discussion. A.L.B., L.H., R.V. and S.R. contributed to the study design and critical discussion. S.H. contributed to all components of the study.

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Conflict of interest

None.

Disclaimer

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