

Overcoming vulnerability by editing the germline? Human germline genome editing in the light of vulnerability ethics

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The concept of vulnerability has become widely acknowledged as a fundamental concept for medical ethics and research ethics, yet rarely considered with respect to ethical assessments of human germline genome editing. A first aim of this paper is to make vulnerability ethics considerations fruitful for issues related to these technical innovations. The possibility of altering the genome promises to overcome forms of vulnerability inherently connected to our existence as physical beings and would hence allow to increase the resilience of human nature or even to move evolution forward by equipping people with new character traits and enhanced capabilities. I suggest a more fine-grained distinction of various applications purposes than the dichotomy of therapeutic and enhancement. I support the rejection of most application purposes as 'therapeutic' and claim that framing them as 'therapeutic' in the context of the current discursive constellation runs the risk of accentuating existing vulnerabilities. With respect to intergenerational responsibilities, I reject the view that editing the germline necessarily leads to corrupt intergenerational relations based on which it must be categorically excluded. I conclude that it is nevertheless important to take a very close look at the challenges that arise, especially from a vulnerability perspective, before irreversible facts are created overhastily.

1. Introduction¹

The concept of vulnerability has gained wide acknowledgment as a fundamental concept for medical ethics and research ethics over the last two decades.² As our bodies are susceptible to numerous diseases and physical ailments, the ability to increase our resilience against such 'plagues of humanity' as serious hereditary diseases by precisely modifying the human genome has given rise to hopes for better and sustainable protection

¹ This article was supported by the University Research Priority Program "Human Reproduction Reloaded" of the University of Zurich.

² For a thorough overview cf. Hank ten Have, *Vulnerability. Challenging Bioethics* (London: Routledge, 2016).

against them, since we might become enabled to treat them causally instead of merely soothing their symptoms. Moreover, the possibility of altering the genome also promises to overcome other forms of vulnerability inherently connected to our existence as physical beings and would hence allow to move evolution forward by equipping people with new character traits and enhanced capabilities.³ Notwithstanding this apparent suitability, the concept of vulnerability has so far hardly found explicit let alone overarching thematization in the specific context of human germline genome editing (= HGGE), or has been considered focusing mainly on questions related to further research.⁴ The general motivation of this paper is to contribute to a broader reception of vulnerability ethics in the context of germline genome editing. I try to achieve this by looking at various application purposes from an ethical perspective based on a nuanced concept of vulnerability. Nevertheless, methodically, the following investigations have a strongly exploratory character, insofar as I try to show that and to what extent the vulnerability perspective can be ethically meaningful for the analysis and articulation of some challenges that arise in connection with the possibility of germline genome editing and that go beyond a purely safety- and efficacy-centred approach.

I proceed as follows: First, in a discussion of relevant literature, I briefly develop a theoretical and ethically meaningful concept of vulnerability, which, in the interest of better analytical clarity, I differentiate into various dimensions. Then I distinguish between different possible applications of germline genome editing and point out the technical challenges and the current state of the international debate. In the main section, I bring the two strands together and consider the various applications from the perspective of the previously developed vulnerability taxonomy. In doing so, I try to show that the vulnerability perspective proves suitable for considering different ethically relevant dimensions of germline modification under a unified conceptual paradigm, while at the same time articulating in a differentiated way different ethical challenges that go beyond safety and effectiveness considerations. In terms of content, I draw attention to some problems related to HGGE by way of example, arguing firstly that in particular the widespread assumption that HGGE is a 'therapeutic' procedure runs the risk of accentuating existing vulnerabilities, while secondly, with regard to the question of the changes in intergenerational relations that HGGE entails, I reject the view that this must necessarily give rise to an argument on the basis of which HGGE must be categorically excluded.

2. The ethical concept of vulnerability

To introduce the concept of vulnerability, I begin by drawing on the account of Martha Fineman⁵, which she developed against the backdrop of how the individual is conceptualized in traditional liberal political philosophy.⁶ This tradition, she argues, is

³ Cf., e.g., John Harris, *Enhancing Evolution: The Ethical Case for Making Better People* (Princeton: Princeton University Press, 2011).

⁴ Markus Labude *et al.*, 'Vulnerability and the Ethics of Human Germline Genome Editing', *The CRISPR journal* 5:3 (2022), pp. 358-363.

⁵ First developed in Martha Albertson Fineman, 'The Vulnerable Subject: Anchoring Equality in the Human Condition', *Yale Journal of Law & Feminism* 20:1 (2008), pp. 8-40.

⁶ For Fineman vulnerability serves as the starting point for a more adequate conception of persons, which in turn provides the basis for an alternative political theory. Fineman's critique is one of a series of criticisms of the self-sufficient subject of liberal individualism, voiced especially by authors of communitarian or feminist perspectives as, e.g., Michael J. Sandel, *Liberalism and the Limits of Justice*

based on a too narrow conception of persons as self-reliant, independent, autonomous subjects and, thus, fails to capture the full range of human experience and development:

„S/he can only be presented as an adult. As such, the liberal subject stands not only outside of the passage of time, but also outside of human experience. The construction of the adult liberal subject captures only one possible developmental stage—the least vulnerable—from among the many possible stages an actual individual might pass through if s/he lives a “normal” lifespan.”⁷

Fineman, by contrast, sees vulnerability as the foundational aspect of human existence inherent in our embodiment. For an even more nuanced understanding of vulnerability, the taxonomy proposed by Rogers and her colleagues is helpful in distinguishing different layers of vulnerability.⁸ The “inherent vulnerability”⁹ essential to all corporeal beings exposes us to the possibility of harm and misfortune from adverse events, both accidental and intentional. Although the possibility of harm is not a necessary condition, the disposition to experience harm is inherent to bodily life. While individuals can take steps to mitigate these risks, they cannot eliminate them entirely.¹⁰ Age, gender, health status, and disability are important determining factors and influence how and in what intensity inherent vulnerability is manifest in different individuals since they modulate the extent to which vulnerability is realized.¹¹

The human condition, thus, is characterized by vulnerability, which brings about the “ever-constant possibility of dependency”¹² and the need for care.¹³ Dependency is a special form of vulnerability where individuals rely on others for their needs and the development of their autonomy.¹⁴ This “situational vulnerability”¹⁵ determines the extent to which we are affected by harm and our ability to cushion it. It is influenced by the resources available to us, both at the individual and societal levels. While vulnerability is universal, it is also unique to each person and influenced by the quantity and quality of resources of which they can make use.¹⁶ No individual can completely avoid ever becoming vulnerable or dependent. Society’s solidarity mechanisms help mediate,

(Cambridge: Cambridge University Press, 1982), Charles Taylor, *Sources of the Self: The Making of the Modern Identity* (Cambridge, Mass.: Harvard University Press, 1989), Eva Feder Kittay, *Love's Labor: Essays on Women, Equality, and Dependency* (New York: Routledge, 1999), Alasdair MacIntyre, *Dependent rational animals: Why human beings need the virtues* (Chicago: Open Court, 1999).

⁷ Fineman, ‘The Vulnerable Subject’, p. 11f.

⁸ Wendy Rogers, Catriona Mackenzie, Susan Dodds, ‘Why bioethics needs a concept of vulnerability’, *International Journal of Feminist Approaches to Bioethics* 5:2 (2012), pp. 11-38.

⁹ Rogers *et al.* ‘Why bioethics’.

¹⁰ Fineman, ‘The Vulnerable Subject’, p. 9.

¹¹ Catriona Mackenzie, ‘The Importance of Relational Autonomy and Capabilities for an Ethics of Vulnerability’, in *Vulnerability: New Essays in Ethics and Feminist Philosophy*, edited by Catriona Mackenzie, Wendy Rogers, and Susan Dodds. New York: Oxford University Press, 2014, 33-59, p. 38.

¹² Fineman, ‘The Vulnerable Subject’, p. 9.

¹³ For Fineman, dependency is a mostly temporary (though possibly long-lasting), certainly not necessarily permanent, property that does not affect everyone equally, while she sees vulnerability as a necessary, universal, ontological constant.

¹⁴ Susan Dodds, ‘Dependence, Care, and Vulnerability’, in *Vulnerability: New Essays in Ethics and Feminist Philosophy*, edited by Catriona Mackenzie, Wendy Rogers, and Susan Dodds. New York: Oxford University Press, 2014, pp. 181-203, p. 183.

¹⁵ Rogers *et al.* ‘Why bioethics’.

¹⁶ Fineman, ‘The Vulnerable Subject’, p. 10.

compensate, and erase vulnerability through policies, programs, and institutions, thereby strengthening individual resilience.¹⁷

Because situational vulnerability is tied to social interactions, there is also the possibility that the social and political structures organized in response to and to mitigate the effects of vulnerability may themselves lead to the creation of new vulnerabilities or to the amplification, prolongation, or perpetuation of existing ones. This can lead to the creation of “pathogenic vulnerability”¹⁸, which includes “all those morally unacceptable vulnerabilities and dependencies which we should, but have not yet managed to, eliminate”.¹⁹ Pathogenic vulnerability can result interpersonally from paternalism, mistreatment, or violence, or be the result of structural injustices such as oppression, domination, or even unconscious prejudice.

Hence, to address vulnerability without exacerbating existing vulnerabilities, guiding principles are necessary. Contrary to Fineman, I do not support the view that the concept of vulnerability should replace the concept of autonomy but rather agree with those who maintain the continuing importance of the concept of autonomy for the ethics of vulnerability.²⁰ Neglecting autonomy can lead to paternalism and new forms of vulnerability. Therefore, promoting autonomy and empowering self-determined action should be a central aim in responding to vulnerability. The concepts of autonomy and capabilities thus serve as guiding principles for interventions aimed at mitigating vulnerability and enhancing resilience.²¹

Finally, the concept of vulnerability extends beyond physical, psychological, and social aspects to include moral vulnerability. This refers to the potential threats to one's autonomy, dignity, and integrity. Every individual, regardless of their status, possesses dignity and should be respected.²² Respecting the integrity, autonomy, and dignity of others goes beyond non-interference; it also involves providing assistance to help them realize their potential.²³ Vulnerability is not just a descriptive concept; it carries normative implications. When someone is harmed or at risk of harm, action must be taken to prevent or rectify the situation.²⁴ Both inherent and situational vulnerability give rise to moral and political responsibilities. These responsibilities include supporting those who are currently vulnerable and reducing the risks that certain individuals, groups, and populations face. Targeted interventions aimed at addressing specific vulnerabilities can help mitigate occurrent vulnerabilities. Overall, recognizing and addressing vulnerability is essential for creating a society that promotes dignity and autonomy for all individuals.²⁵

¹⁷ *Ibid.*

¹⁸ Cf. Rogers *et al.*, ‘Why bioethics?’.

¹⁹ Robert E Goodin, *Protecting the vulnerable. A reanalysis of our social responsibilities* (Chicago and London: Chicago University Press, 1985), p. 203; ten Have, *Vulnerability*, at p. 203.

²⁰ Cf. Mackenzie, ‘The Importance of Relational Autonomy’; Corine Pelluchon, *L'autonomie brisée. Bioéthique et philosophie* (Paris: Presses Universitaires de France, 2008); Corien Pelluchon, ‘Taking Vulnerability Seriously: What Does It Change for Bioethics and Politics?’, in *Human Dignity of the Vulnerable in the Age of Rights*, edited by Aniceto Masferrer and Emilio García-Sánchez. Cham: Springer, 2016, pp. 293-312; Paul Ricoeur, ‘Autonomy and vulnerability’, in *Reflections on the Just*, translated by Dave Pellauer (Chicago: University of Chicago Press, 2007), pp. 72-90.

²¹ Mackenzie, ‘The Importance of Relational Autonomy’, p. 45.

²² Jacob D. Rendtorff, ‘Basic ethical principles in European bioethics and biolaw: autonomy, dignity, integrity and vulnerability - towards a foundation of bioethics and biolaw’, *Medicine, health care, and philosophy* 5:3 (2002), pp. 235-244, p. 243.

²³ *Ibid.*

²⁴ ten Have, *Vulnerability*, p. 129.

²⁵ Rogers *et al.*, ‘Why bioethics’, p. 25

Healthcare and medicine are obviously permeated by phenomena of vulnerability. Their very *raison d'être*, disease and illness, are visible signs of the physical (yet also psychological and social) vulnerability of human beings. It comes as no surprise that overcoming vulnerability has often played a crucial role as a driving motivation for those who argue that methods that allow intervening in the human genome promise to become a powerful tool to strengthen human resilience since in medical contexts vulnerability frequently refers to states that ought to be overcome.²⁶ Medical progress is, therefore, for many synonymous with the development of therapies and treatment approaches that allow for the reduction, elimination, or prevention of physical vulnerabilities. In diseases based on pathological mechanisms on the molecular level of the genome technologies that allow to precisely target, correct, or alter the disease-causing molecular structures appear to be particularly appealing to increase resilience and reduce vulnerability. The discovery of CRISPR-Cas²⁷ technology has fuelled such old hopes²⁸ of curing diseases through direct intervention in the genome and has also given new impetus to the debate about which applications should ethically, legally, and socially be acceptable. To be able to shed light on these questions from a vulnerability ethics perspective, it is first necessary to have a more precise picture of the technical possibilities and the various fields of application.

3. Genome editing: technique, applications, ethical debate

A first fundamental and ethically relevant distinction between different forms of genome editing must be drawn with respect to the targeted tissue type: whether the cells whose genetic material is changed are somatic cells (basically any tissue cell including blood cells) or cells of the germ line (i.e., sperms, oocytes, and their respective precursor cells, and fertilized oocytes).²⁹

3.1. Genome editing in somatic and germline cells

It is largely undisputed that therapeutic applications in somatic cells are to a much lesser extent regarded as ethically, legally, or socially problematic if they meet the standards of safety, benefit-risk ratio, and effectiveness that usually apply to medical treatments. In their character as therapeutic applications on living persons, they are, in principle, capable of fulfilling the requirement of informed consent of the treated person. Genome modification in somatic cells is limited locally or to a certain type of cells or tissue. They can, in principle, be interrupted, and are (potentially) reversible. Moreover, the induced genetic modification is limited to the organism of the respective patient and not passed on to the offspring. Provided that the usual safety standards of medical therapies are met, and the informed consent of the patient is available, there is nothing fundamentally opposing

²⁶ Joachim Boldt, 'The concept of vulnerability in medical ethics and philosophy', *Philosophy, Ethics, and Humanities in Medicine* 14:6 (2019).

²⁷ Martin Jinek *et al.*, 'A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity', *Science* 337:6096 (2012), pp. 816-821. Jennifer A. Doudna and Emmanuelle Charpentier, 'Genome editing. The new frontier of genome engineering with CRISPR-Cas9', *Science* 346:6213 (2014), 1258096.

²⁸ Cf. Theodore Friedmann and Richard Roblin, 'Gene therapy for human genetic disease?', *Science* 175:4025 (1972), pp. 949-955.

²⁹ Cf. Edward M. Berger and Bernard M. Gert B. 'Genetic disorders and the ethical status of germ-line gene therapy', *The Journal of medicine and philosophy* vol. 16:6 (1991), pp. 667-683.

their use. Consequently, there are several therapies approved for or undergoing clinical trials.³⁰

The situation is fundamentally different, however, for applications in the germline which aim at changing the genetic material passed on to the offspring.³¹ The ethical challenges are fundamentally different in nature: There is no person suffering from an illness and therefore dependent on medical therapy, but an embryo, from which a child develops, is created in the first place as part of the procedure.³² It is, therefore, also different from pediatrics or neonatology where parents or next of kin can provide proxy consent to medical procedures. All decisions have to be made by the prospective parents and would have to take place in a hypothetical space about possible effects that would affect a potential future child, which raises questions about the best interests of the child and the justifiability of selective reproduction. Furthermore, an intervention in germline cells would not only affect the person growing from it, but would be passed on to her offspring, and would hence affect the genome of the human population, which underlines the importance of a thorough and society-wide debate on various scopes of applications.

In their extensive review of the ethical implications of HGGE, the National Academy of Sciences and the Royal Society, sketch a translational pathway for various application purposes. But they leave open the question of which purposes HGGE could be deemed acceptable.³³ To get an idea of various purposes HGGE can serve I shall briefly sketch them before going on to discuss them in light of the involved vulnerabilities.

3.2. Purposes of genome editing in the germline

In the literature, the different applications of HGGE are usually distinguished either as therapeutic and therefore acceptable or as enhancement and therefore problematic. The dichotomy of therapy and enhancement is often too simplistic for biomedical applications, and especially in the context of genetic interventions. I give two reasons for this claim: First, in the literature on HGGE, 'therapeutic' is usually used to describe the modification of the germline in descendants of parents who are carriers of a severe genetic condition, yet, as seen, this is a problematic use of the term. Second, 'enhancement' is usually used to describe treatments that go beyond what is necessary to restore or sustain good health.³⁴

³⁰ The continuously updated website <https://crisprmedicineneeds.com/clinical-trials/> (accessed 2022-11-09), run by Danish company COBO Technologies, lists over hundred gene editing studies (including other modalities than CRISPR like Zinc Finger Nucleases, TALENs, MegaTALS, CAS-CLOVER, MegaNuclease) that have advanced to clinical trials over 60 based on CRISPR. For various examples of medical application see also Mohammed F. Rasul *et al.*, 'Strategies to overcome the main challenges of the use of CRISPR/Cas9 as a replacement for cancer therapy', *Molecular Cancer* 21:64 (2022).

³¹ The first experiment with CRISPR-Cas9 on human embryos was reported in 2015; the authors demonstrated that the GE system performed targeted cleavage in the β -globin gene, which when mutated causes β -thalassaemia. Puding Liang *et al.*, 'CRISPR/Cas9-mediated gene editing in human triprounuclear zygotes', *Protein Cell* 6:5 (2015), pp. 363-372.

³² Cf. Roberto Andorno *et al.*, 'Geneva Statement on Heritable Human Genome Editing: The Need for Course Correction', *Trends Biotechnology* 38:4 (2020), pp. 351-354, p. 352. Christoph Rehmann-Sutter, 'Why Human Germline Editing is More Problematic than Selecting Between Embryos: Ethically Considering Intergenerational Relationships', *The New Bioethics* 24:1 (2018), 9-25.

³³ National Academy of Medicine, National Academy of Sciences, and the Royal Society. *Heritable Human Genome Editing* (Washington, DC: The National Academies Press, 2020), p. 96

³⁴ Cf. Eric T. Juengst, 'What Does Enhancement Mean?', in *Enhancing Human Traits: Ethical and Social Implications*, edited by Erik Parens (Washington, D.C.: Georgetown University Press, 1998), pp. 29-47, at p. 29. Or similarly and more recently Catherine Gee, 'What is Enhancement?', *Journal of Cognition and Neuroethics* 3:4 (2016), pp. 41-54.

But, as the case of vaccines illustrates, many treatments can be necessary to sustain good health but are at the same time applied to “perfectly normal and perfectly healthy human beings”, which justifies calling them “enhancements”.³⁵ We, therefore, need a more nuanced account of the various purposes germline genome editing can serve since modifications of the human germ line can be associated with different goals, aim at different target structures, produce different effects (intended and unintended), and be associated with different methods, which leads to different ethical questions in each case.

In the following, I will distinguish between genetic germline modifications that a) aim at the therapy of infertility, b) aim at the correction of a pathogenic gene to achieve normal function in the potential offspring, c) aim at the modification of a gene to introduce a variant into the genome that is considered to lead to better health conditions (health-based enhancement), and d) wish-fulfilling enhancement beyond medical benefit.³⁶

a) Therapeutic purposes

The term therapy usually presupposes that there is a subject with a need that can be overcome by a certain treatment. Both are true in infertile adults, and therefore infertility treatments are one possible realm of *therapeutic* applications of germline genome editing.³⁷ When infertility is caused by a genetic mutation in germline cells with the effect that no fertilizable gametes can be produced, genetically modifying the mutation that causes infertility in gamete precursor cells might be an option to restore reproductive capabilities in infertile couples. Since idiopathic infertility is thought to have a genetic component in half of cases³⁸, infertility treatment by editing the germ cells could once become a welcomed approach to individualized therapy.³⁹ Examples in male patients are non-obstructive azoospermia, where spermatogonial stem cells would need to be genetically altered to pass the altered genetic material to all mature spermatozoa and progeny, and would allow the production of mature spermatozoa either using stem cells or by gene therapy.⁴⁰ An example of therapeutic germline gene editing in infertile female patients is the missense mutation TUBB8 which causes oocytes to undergo developmental arrest after fertilization.⁴¹ Genetically correcting the missense mutation TUBB8 in premature oocytes could recover their developmental potential. Both applications are still in the experimental stage.⁴² Another, yet clinically approved, therapy that involves modification of the germline is mitochondrial replacement therapy, where nuclear genetic material is moved from an egg or single-cell embryo with dysfunctional mitochondria to a donor egg that has

³⁵ Harris, *Enhancing Evolution*, p. 21.

³⁶ Since every conceptual definition also relies on evaluative assumptions, to distinguish therapy from enhancement thoroughly, a case by case discussion with broad public engagement would be necessary. Cf. National Academies of Sciences, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance* (Washington, DC: The National Academies Press, 2017), p. 176f.

³⁷ Giovanni Rubeis and Florian Steger, ‘Risks and benefits of human germline genome editing: An ethical analysis’, *Asian Bioethics Review* 16:10 (2018), pp. 133-141.

³⁸ Priti Singh and John C. Schimenti, ‘The genetics of human infertility by functional interrogation of SNPs in mice’, *Proceedings of the National Academy of Sciences of the United States of America* 112:33 (2015), pp. 10431-10436.

³⁹ Tetsuya Ishii, ‘Reproductive medicine involving genome editing: clinical uncertainties and embryological needs’, *Reproductive BioMedicine Online* 34:1 (2017), pp. 27-31.

⁴⁰ Sarah C. Vij, Edmund Sabanegh Jr., Ashok Agarwal, ‘Biological therapy for non-obstructive azoospermia’, *Expert Opinion on Biological Therapy*. 18 (2018), pp. 19–23.

⁴¹ Ruizhi Feng *et al.*, ‘Mutations in TUBB8 cause a multiplicity of phenotypes in human oocytes and early embryos’, *Journal of Medical Genetics* 53 (2016), pp. 662-671.

⁴² Ishii, ‘Reproductive medicine’.

had its nuclear genetic material removed.⁴³ Since mitochondria in maternal gamete cells are transmitted to offspring stemming from these cells, the mitochondrial DNA they contain is passed on to the offspring as well, wherefore the procedure qualifies as germline therapy.

b) Correcting a pathogenic trait

Germline modifications that aim at correcting a pathogenic version of a gene to restore normal function in the offspring of parents, of which at least one is a carrier of a severe hereditary genetic disorder, are the most discussed applications of HGGE. They are sometimes called ‘therapeutic’ which is not without conceptual difficulties, because, as mentioned above, there is no patient in need of therapy.⁴⁴ It would rather be convincing to consider them as a subset of enhancement, e.g., “disease prevention-enhancement”⁴⁵. However, the aim is to make it possible for future parents to have children that are genetically related to both parents even if at least one partner is a carrier of a severe genetic disease that would most likely be passed on to a child conceived from the gametes of the future parents.

c) Health-aimed enhancement

Health-aimed enhancement aims at modifying the genome of the offspring in a way to prevent a phenotype that could have less adverse, but not life-threatening, health effects by replacing genetic sequences with other sequences, that are naturally occurring in the population. This form of enhancement can be seen as a form of “normal range human enhancement” because it might be narrowed down by introducing so-called ‘wild-type’ alleles that occur naturally in the population.⁴⁶ The genetic modification performed on the first babies born after HGGE was of this kind.

It is often preventive enhancement and could be motivated by various reasons: To replace naturally occurring, but disadvantageous alleles with better alternatives and thus facilitate better metabolic functions, adapt the human organism to changing environmental circumstances such as providing resistance to infectious pathogens or other potential threats due to changing physical environment such as, e.g., climate change.

d) Wish-fulfilling enhancement beyond medical benefit

Some of the strategies of wish-fulfilling enhancement beyond medical benefit include producing a certain ability in the offspring by introducing a rare allele of a specific gene known or believed to be associated with a desired phenotype (e.g., the constitutive activation of the EPO gene has been proposed to confer advantages in endurance sports),

⁴³ Ewen Callaway, ‘First UK children born using three-person IVF’, *Nature* 617 (2023), pp. 443-444.

⁴⁴ These applications are sometimes called “therapeutic”, which is not without conceptual difficulties, because there is no patient in need of therapy, cf. Tina Rulli, ‘Reproductive CRISPR does not cure disease’, *Bioethics* 33:9 (2019), pp. 1072-1082, in contrast to César Palacios-González, ‘Reproductive genome editing interventions are therapeutic, sometimes’, *Bioethics* 35:6 (2021), pp. 557-562.

⁴⁵ This category is sometimes considered to be a subset of enhancement, namely “disease prevention-enhancement”, cf. Emilia Niemiec and Heidi Carmen Howard, ‘Ethical issues related to research on genome editing in human embryos’, *Computational and structural biotechnology journal* 18 (2020), pp. 887-896.

⁴⁶ Cf. Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: social and ethical issues* (London: Nuffield Council on Bioethics, 2018), p. 70 and p. 92, and Guy Kahane and Julian Savulescu, ‘Normal human variation: refocussing the enhancement debate’, *Bioethics* 29 (2015), pp.133-143.

modifying traits such as height or cognitive ability that are influenced by hundreds or thousands of genetic variants across the genome. They might often be 'innovative' as it could involve introducing new variants into the genome, that is alleles or genes that are naturally not or only rarely occurring in a given population, and that progeny would not have been able to receive through sexual or assisted reproduction. There are many goals these *innovative enhancement* strategies could strive for including attempts to acquire new genetic traits that have not been part of human DNA during the development of mankind but are supposed to be beneficial, such as, for instance, resistance to radiation exposures encountered during extended spaceflight.

The four categories differ in terms of the goal to be achieved by germline intervention. The difference between a) and b) to d) is that in a) the beneficiaries are the infertile adults, whereas b) to d) aim at creating offspring with certain traits that are expected to be beneficial to them. b) and c) are not categorically distinct but only qualitatively, b) aims at correcting a genetic disorder with life-threatening consequences, whereas c) is about genetic traits without life-impairing impact, while in d) health is not a primary issue.

They can also be distinguished in terms of the layer of vulnerability addressed and the individuals affected by them. While categories a) to c) can be understood as means to overcome inherent vulnerabilities, because they target structures that have a direct influence on the normal physiological function of the organisms, health benefits are not the primary intention of applications in category d). Nevertheless, they can be envisaged as a response to situational vulnerabilities: in many societies, for example, it may be advantageous to be born a white male with a high IQ. I will come back to the question of evaluating these different applications below and will now first point out the technical challenges that still exist.

3.3. Technical challenges of HGGE and the state of the ethical debate

Regardless of the wide range of possible applications, several technical hurdles such as safety, effectiveness, appropriateness, and cost-efficiency must still be overcome before thinking about possible translational pathways.⁴⁷

The first problem is related to the accuracy of genome editing. Undesired modifications can occur outside of the targeted sequence (off-target) or within or next to the targeted sequence (on-target), both leading to unintended changes in the genetic code. Unintended changes do not necessarily lead to a problematic health condition. They can be silent, i.e., they don't alter the sequence of amino acids and hence don't change the function of the resulting protein. But they can also affect the expression of a gene when a) the DNA change also alters the amino acid sequence (missense mutation⁴⁸), b) the DNA modification creates a premature stop codon which truncates the polypeptide the DNA sequence codifies for (nonsense mutation)⁴⁹, or c) the insertion or deletion of a DNA base alters the reading frame of the gene which may have various effects as, e.g., unfunctional proteins or dysregulation of the cellular translational process (frameshift mutation⁵⁰).

⁴⁷ Don P. Wolf *et al.*, 'Principles of and strategies for germline gene therapy', *Nature Medicine* 25 (2019), pp. 890-897.

⁴⁸ Sickle cell anaemia is an example of a disease caused by a substitution of a single DNA base (GAG → GTG ; Glu → Val).

⁴⁹ Cystic fibrosis can, among other possible causes, result from a nonsense mutation.

⁵⁰ Crohn's disease can be caused by a frameshift mutation.

Another type of problem is increased mosaicism due to genome editing: When HGGE is performed on multicellular embryos, the targeted modification is not equally effective in all cells.⁵¹ This may result in cell lines with (slightly) different DNA sequences (genotypes), which in turn might lead to different cell phenotypes or cell behavior. Mosaicism, which also occurs spontaneously⁵² and is supposed to be very common⁵³, can, but doesn't have to, increase the risk of autoimmune diseases.⁵⁴ In fact, healthy babies with correct chromosome numbers can be born from mosaic embryos.⁵⁵

In accordance with these still high technical hurdles, there seems to be widespread international consensus in the scientific community that clinical applications of HGGE are inappropriate.⁵⁶ However, there is no consensus (anymore) on the question of whether germline applications are merely premature at this stage of development of the technique, its accuracy, potential risks, and long-term implications, or whether there are categorical reasons prohibiting germline interventions. Based on risk-benefit considerations some people categorically call for a complete international ban on this research⁵⁷, while others opt for a temporary moratorium.⁵⁸ Yet, there seems to be growing consensus that if studies based on a significant cohort of edited human embryos can provide preclinical evidence of safety and efficacy and demonstrate that the procedure can generate and select, with high accuracy, suitable numbers of viable embryos, HGGE may be considered safe enough for initial clinical use.⁵⁹ As I will argue in the following section, technical questions of safety and effectiveness cannot be the sole deciding factor in the evaluation of possible applications of HGGE. As an evaluation from a vulnerability perspective shows, HGGE brings with it numerous other ethical challenges.

4. Relevant vulnerabilities in reproductive germline editing

As we have seen earlier, we have to distinguish various layers and dimensions of vulnerability. Inherent vulnerability is an essential feature of embodied life and depends on various factors, including age, gender, health status, and disability. Given the possibility of reducing the genetic causes of serious diseases, or more generally, factors

⁵¹ Maryam Mehravar *et al.*, 'Mosaicism in CRISPR/Cas9-mediated genome editing', *Developmental Biology* 445:2 (2019), pp. 156-162.

⁵² Cery E. Currie *et al.*, 'The first mitotic division of human embryos is highly error prone', *Nature Communications* 13:6755 (2022).

⁵³ Evelyne Vanneste *et al.*, 'Chromosome instability is common in human cleavage-stage embryos', *Nature Medicine* 15 (2009), pp. 577-583.

⁵⁴ Barbara R. Migeon, 'The role of X inactivation and cellular mosaicism in women's health and sex-specific diseases', *Journal of the American Medical Association* 295:12 (2006), pp. 1428-1433.

⁵⁵ Currie *et al.*, 'The first mitotic division'.

⁵⁶ Cf. Carolyn Brokowski, 'Do CRISPR Germline Ethics Statements Cut It?', *The CRISPR journal* 1:2 (2018), pp. 115-125.

⁵⁷ Jeffrey R. Botkin, 'The case for banning heritable genome editing', *Genetics in Medicine* 22 (2020) pp. 487-489.

⁵⁸ Eric S. Lander *et al.*, 'Adopt a moratorium on heritable genome editing', *Nature* 567: 7747 (2019), pp. 165-168.

⁵⁹ The studies should show that embryos have the intended edit(s) and no other modification at the target(s); lack additional variants introduced by the editing process at off-target sites—that is, the total number of new genomic variants should not differ significantly from that found in comparable unedited embryos; lack evidence of mosaicism introduced by the editing process; are of suitable clinical grade to establish a pregnancy; and have aneuploidy rates no higher than expected based on standard assisted reproductive technology procedures. Cf. National Academies, *Heritable Human Genome Editing*.

that increase inherent vulnerability, editing the germline appears to hold considerable potential for improving human resilience in general and – presumably – quality of life. Some argue that, if germline genome editing were once safely and effectively possible, the principle of procreative beneficence would imply a duty to edit the genome of the offspring.⁶⁰

However, the question of whether the consequences of HGGE can be regarded as predominantly beneficial or predominantly harmful is one of the most challenging problems for the ethical evaluation of HGGE. This is also because the question must be answered very differently depending on the goal HGGE is meant to achieve, the method used, and the possible outcomes.

HGGE procedures that aim at the treatment of a) infertility, b) the correction of a genetic disorder, or c) enhancements that promise to prevent susceptibility to not life-threatening health conditions basically promise to improve inherent resilience by fundamentally or gradually decreasing inherent vulnerabilities.

However, germline interventions aimed at overcoming situational vulnerabilities, such as height, muscle strength, or complex features such as intelligence (category d)), seem highly problematic, as they take certain contingent societal values and structural inequalities as an occasion to adapt the genome to them. This does not seem to be a convincing motive or justification, given the fact that the induced changes occur *in the germline* and are thus preserved far beyond the first generation of offspring, while social conditions are subject to constant change. The induced modification might, therefore, prove detrimental already in the first generation of offspring. It also seems to be the wrong tool to change the germline when social structures could be changed with the effect of enabling instead of disabling people. Since it seems morally dubious, I will therefore not pursue this form of HGGE any further.

From a public health perspective, it can be argued that safe and effective germline modification for a large variety of genetic conditions with more and less impact on health may significantly reduce the overall burden of disease and hence public health care costs, which then might free up public or health care resources that can be redirected to other people in need of support. It is doubtful, however, that state policies to promote HGGE can be designed in such a way that they do not lead to the problematic discriminations of the type of authoritarian eugenics of the first half of the 20th century and thus become the origin of new pathogenic vulnerability. If we want to remain true to the values of a human rights-based liberal society, reproductive choices must be left to the autonomy of individuals, as long as their decisions do not lead to harm to others (i.e., in the first place, their offspring) or society. We must therefore look more closely at the prospective parents and future children.

As seen in the therapy case a), some infertile couples could potentially benefit from HGGE. Provided that these procedures can be used so precisely that the technical intervention would merely restore the normal functionality of the gamete cells without having any other effects, such applications would also have no ethically relevant influence

⁶⁰ Julian Savulescu, 'Procreative Beneficence: Why We Select the Best Children', *Bioethics* 15:5-6 (2002), pp. 413-426; Savulescu, Julian and Guy Kahane. 'The Moral Obligation to Create Children with the Best Chance of the Best Life', *Bioethics* 23:5 (2009), pp. 274-290; Marcelo de Araujo, 'Editing the genome of human beings: CRISPR-Cas9 and the ethics of genetic enhancement', *Journal of Evolution and Technology* 27 (2017), pp. 24-42; Harris, *Enhancing evolution*; Christopher Gyngell, Hilary Bowman-Smart, and Julian Savulescu, 'Moral reasons to edit the human genome: picking up from the Nuffield report', *Journal of Medical Ethics* 45 (2019), pp. 514-523.

on future offspring. The relevant counterfactual would simply be that no child would be born, or, if the parents were to switch to the alternative use of donor gametes instead of HGGE, that another child would be born. HGGE to restore fertility is, in Derek Parfit's framework⁶¹, only identity affecting⁶², not person affecting⁶³, with the consequence that children born from the procedure could neither benefit nor be harmed by it.

It is, however, different with applications that aim at changing the genome in a way that leads to a different phenotype in the offspring (categories b) to d)). First, we must remember that this form of HGGE is not a method to "treat, cure, or prevent disease in any existing person."⁶⁴ Rather, it is used to create embryos with a genome altered in a particular way, which are then transferred to a uterus to achieve, after a successful pregnancy, the birth of a child with certain traits chosen by the prospective parents. So, it would be wrong to think of HGGE as a particularly early form of pediatric medicine, but rather as a form of reproductive medicine for parents who want children with certain genetic traits. Vulnerability considerations now come into play on both sides, the parents' and the future child's.

4.1. Direct and immediate vulnerabilities

Given their absolute dependency on their environment, children are quintessentially vulnerable, since they are absolutely dependent on the decisions of their (future) parents. And although they are children of their parents, parents do not own their children. Rather, children depend on parents to exercise their stewardship in the best interest of the child, since (future) children are the ones who must live with the consequences of the decision their (future) parents made. Whether a decision can be regarded as morally acceptable or not, therefore depends on the effects it has on the life of the future children.

In prospective parents who are carriers of a genetic disease, and who could generate only embryos that carry a disposition for developing a potentially lethal disease, their desire for 'healthy' genetically related offspring makes them especially dependent, and thus vulnerable, on the possibilities of medically assisted reproduction. We do not need to enter into a debate about the legitimacy of a desire to have children, whatever the cost, but can simply acknowledge that the desire for a genetically related child of one's own is to be valued as a legitimate expression of reproductive self-determination. Methods that allow this wish to be fulfilled should therefore be examined in this respect as potentially valuable means of strengthening the reproductive autonomy of genetically predisposed future parents. Having access to assisted reproduction enhances their reproductive autonomy, and denying them access needs to be justified on solid grounds.

When parents who, despite being carriers of a severe genetic disease, want to give birth to their own genetic children, they have basically two options: negative selection using IVF and PGT, in which as many embryos are conceived in vitro as necessary to have at least one embryo without the disease-causing gene among them, which is then transferred into the uterus. This method of preventing that a sick child is born has the advantage that it does not require any intervention in the genome, which could result in undesirable side effects of an unknown magnitude. The procedure also has limitations: in couples with one parent homozygous for a dominant genetic disorder or when both parents are homozygous for a recessive genetic disease, the disorder will be passed on to

⁶¹ Derek Parfit, *Reasons and persons*. Oxford: Clarendon Press, 1984.

⁶² Parfit, *Reasons and persons*, pp. 356-359.

⁶³ Parfit, *Reasons and persons*, pp. 361-379.

⁶⁴ Andorno *et al.*, 'Geneva Statement', p. 352.

all children, or in situations, where just one parent is a carrier, but it is simply not possible to achieve a suitable number of unaffected embryos for transfer. Even though they are very rare, in such cases, genome editing could produce the desired result of genetically own children without the detrimental hereditary predisposition.

From an ethical perspective, the two procedures differ fundamentally regarding the children born from them. Negative selection by IVF and PGT is ethically neutral for the children born from it: A different child is born in each case, depending on which embryo is selected and transferred. The procedure affects the numerical identity but is not person-affecting. HGGE procedures, on the other hand, do not affect the numerical identity of the child born from them: It is the same child (numerical identity), but it does not have the same properties (qualitative non-identity), because its genetic makeup has been genetically modified. The procedures are therefore person-affecting.⁶⁵ Person-affecting procedures raise the question of whether the resulting child was better off as a result of the treatment compared to a birth without this intervention. This seems to depend crucially on how safe and efficient the treatment is. According to the authors of the *Consensus Report* “the most favorable balance of potential harms and benefits” may be found in “prospective parents for whom there are no available alternatives, and on diseases or conditions for which mortality is high and/or morbidity is severe.”⁶⁶ This seems to lead to the argument that a child that would be affected by a serious genetic disease if it wouldn’t have undergone HGGE, would benefit from genetic modification that corrects the genetic disorder even if there would be a risk of harmful side effects as long as they are considerably less harmful than the genetic disorder prevented by the intervention. But, as has been noted with reference to an earlier statement by the same body, this argument is not convincing because the child will only be born because of the germline modifying procedure. “Seen from the future child’s perspective, the side effects of [H]GGE treatment cannot be justified through comparison with the potential for living with disease or disability, which is prevented.”⁶⁷ Only a minimal risk comparable to the risk every other child faces could be justified.⁶⁸ This sets very tight ethical limits to all attempts to justify HGGE (in all the categories of application differentiated above). They are not categorical limits, however, but hypothetical ones, since they depend essentially on the safety and effectiveness of the technique. It is possible, though possibly not very likely, that the technology will turn out

⁶⁵ Recently, there has been some doubt whether reproductive germline modifications are always person-affecting. Robert Sparrow, ‘Human Germline Genome Editing: On the Nature of Our Reasons to Genome Edit’, *The American Journal of Bioethics* 22:9 (2022), pp. 4-15, argues that, since in probably most cases modifying the genome would involve PGT to make sure the intended editing was successful and without unintended effects that would compromise the suitability of the embryo for implantation, germline modifications will “for the foreseeable future” not be “person affecting” and, therefore, fail “to benefit [or harm] the genome edited individual” (p. 10.). I am not convinced by the argument because it seems to rely on a perspective that only considers the various procedures involved (the “history of events”, *ibid.*). But the ethically relevant perspective, in my opinion, is the “history of the particular embryo that developed into the genome-edited individual” (p. 9), and the ethically relevant question is whether the editing was beneficial to this individual, even if the particular individual that came into existence was selected out of multiple embryos that were grown after the genetic modification. The selection step is identity affecting, but before there was a person affecting step of genetic modification that affected all the embryos grown afterwards, irrespective of whether they would later be implanted or not.

⁶⁶ National Academies, *Heritable Human Genome Editing*, p. 98.

⁶⁷ Rehmann-Sutter, ‘Why Germline Editing is More Problematic’, p. 17.

⁶⁸ *Ibid.*

to be virtually risk-free. Only we do not know that today, and it is questionable whether we ever will if the search for translational pathways were to move within these limits.

However, there is little hope for this assumption. If we look at the ethical debate about HGGE, it seems that the interest in enhancement applications is much greater than that in corrective applications. This is indicated on the one hand by the significantly higher interest in enhancement both in the philosophical and scientific communities⁶⁹, but also by the fact that the field of possible targets is just much larger for enhancement than for such 'therapeutic' purposes and, therefore, financially more attractive for industrial developers of such applications. Unsurprisingly, the first reported germline modifications in humans didn't aim at correcting a pathogenic trait but at conferring resistance against HIV, clearly an enhancement purpose. In addition, the application of HGGE in the context of reproductive treatments of carrier pairs of genetic diseases is, in the majority of these anyway few cases, probably not the best method to achieve the goal of healthy offspring, since there are alternative options such as the use of donor gametes, embryo adoption, or adoption of a child with (at least for now) much lesser risks than HGGE. Given that these alternatives exist, the claim that the case of prospective parents, who would have no success even after several attempts to achieve enough unaffected embryos suitable for transfer, has the "most favorable balance of potential harms and benefits"⁷⁰ seems to be preconceived in a presumably non-neutral way because it is contingent on the assertion that the wish of prospective parents to not use donor gametes has a normative relevance that outweighs (or at least balances) the risks for the child born through HGGE.⁷¹ The depiction of these case situations in this presumably non-neutral manner and framing these situations as 'therapeutic', as it is usually done in the literature, seems to serve the purpose of presenting them in a more morally favorable way, with the actual aim of gaining public approval for at least such 'therapeutic' uses. The underlying logic seems to work something like this: If the safety and effectiveness of the procedures could be proven in these 'therapeutic' cases, other application goals from categories c) and d) would also come into the range of options to be considered. The successful implementation of 'therapeutic' HGGE would then function as a gate-opener to the many more numerous and financially far more lucrative possible enhancement applications. Future parents, who

⁶⁹ Cf. the authors arguing in favor of this application: Nick Bostrom, 'Human Genetic Enhancements: A Transhumanist Perspective', *The Journal of Value Inquiry* 37 (2003), pp. 493-506; George M. Church and Edward Regis, *Regensis: How synthetic biology will reinvent nature and ourselves*. New York: Basic Books (2014); de Araujo, 'Editing the Genome', Ronald M. Green, *Babies by design: The ethics of genetic choice* (New Haven: Yale University Press, 2007); Gyngell, Bowman-Smart, and Savulescu, 'Moral Reasons'; Harris, *Enhancing Evolution*; Russell Powell and Allen Buchanan. 'Breaking evolution's chains: the prospect of deliberate genetic modification in humans', *Journal of Medicine and Philosophy* 36:1 (2011), pp. 6-27; Ingmar Persson and Julian Savulescu, *Unfit for the Future: The Need for Moral Enhancement* (Oxford: Oxford University Press, 2012); Antonio Regalado, 'Engineering the perfect baby', *MIT Technology Review* 118:3 (2015), pp. 27-33; Savulescu, Julian. 'New breeds of humans: the moral obligation to enhance', *Reproductive BioMedicine Online* 10 (2005), pp. 36-39; Savulescu, Julian. 'Genetic interventions and the ethics of enhancement of human beings', *Readings in the Philosophy of Technology* (2009), pp. 417-430; Lee M. Silver, *Remaking eden: Cloning, genetic engineering and the future of humankind* (London: Phoenix, 1999); Kevin R Smith, Sarah Chan, and John Harris. 'Human germline genetic modification: scientific and bioethical perspectives', *Archives of medical research* 43:7 (2012), pp. 491-513; Gregory Stock, *Redesigning humans: Our inevitable genetic future* (Boston: Houghton Mifflin Harcourt, 2002).

⁷⁰ National Academies, *Heritable Human Genome Editing*, p. 98.

⁷¹ Cf. Sparrow, 'Nature of Our Reasons', and Giulia Cavaliere, 'Genome editing and assisted reproduction: Curing embryos, society or prospective parents?', *Medicine, Health Care, and Philosophy* 21:2 (2018), pp. 215-225.

are already burdened by their hereditary disease, are thus exposed to an increased risk that the realisation of their wish for a genetically related child without the hereditary disease is only ostensibly the goal of an HGGE treatment but is actually itself a means to the end of establishing reproductive germline modifications. Such a discursive constellation, then, brings with it the danger that the situation and the risks to be weighed up will be presented to the prospective parents in a manner according to the rules of the discourse. It wouldn't even happen out of malicious intent but just as an effect of such a discursive constellation. An element that supports this view can be found in surveys on the acceptance of HGGE: When people are asked whether they would allow HGGE for 'therapeutic reasons' such as the prevention of severe hereditary genetic disorder in the offspring, reference to possible alternatives such as donor gametes is very rare and, additionally, the media hardly ever talk about IVF & PGT as a possible alternative to HGGE.⁷² Eventually, the already inherently vulnerable prospective parents, due to their dependence on access to appropriate fertility treatment (including adequate information), become additionally vulnerable to exploitation by research interests in a highly competitive field influenced by the "promise of scientific fame and immense grant-funding in a multibillion-dollar industry [...] for scientists developing this technology."⁷³

If prospective parents are recruited for the motivation of achieving research success, they may be at risk of not being adequately informed about the risks of using HGGE and thereby not giving their consent appropriately informed. This risk is significant since epistemic hurdles are high due to the complex matter at hand. The complexity of the biotechnology involved, the knowledge of biological interactions, and the understanding of statistical probabilities necessary to make a truly informed decision clearly demonstrate the dependence of prospective parents on numerous situational factors (educational background, access to information, financial opportunities, social inclusion, etc.) and may easily lead to epistemic and moral overload.

From a vulnerability perspective, HGGE has, therefore, a high risk of exacerbating existing vulnerabilities and creating new vulnerabilities on various levels: Unsafe germline modifications would increase inherent vulnerability and probably violate the dignity and integrity of future children, and the discursive interest in "revolutionary techno-scientific breakthroughs"⁷⁴ through HGGE is highly probable to contribute to an increase of prospective parents' situational and moral vulnerability.

4.2. *Intergenerational vulnerabilities*

The future parents' decision to use HGGE not only influences the life of the future child but also actively influences the framework for the future child's own reproductive decisions when he or she reaches reproductive age because the hereditary changes brought about will also be passed on to their offspring. With respect to the direct descendants, this can be seen as a problematic predetermination of children's living conditions brought about by the parents' decision to have a child through HGGE, which may conflict with children's right to an open future. In view of the unknown possible long-term effects of the method, it would be irresponsible not to accompany and monitor children born by means of an HGGE procedure over a longer period (or even lifelong) in order to be able to provide them with support as quickly as possible should any undesirable health effects occur.

⁷² Marcy Darnovsky, and Katie Hasson, '2020. CRISPR's Twisted Tales: Clarifying Misconceptions about Heritable Genome Editing', *Perspectives in Biology and Medicine* 63:1 (2020), pp. 155-176, p. 167.

⁷³ Labude *et al.*, 'Vulnerability', p. 360.

⁷⁴ Darnovsky and Hasson. 'CRISPR's Twisted Tales', p. 159.

Having to adhere to such a plan can be perceived as a significant restriction of one's freedom and can easily conflict with the realisation of one's life dreams.

Accepting such consequences might amount to an instrumentalization that violates the dignity of the (future) child for the purpose of fulfilling the wishes of the (future) parents for a child of their own. This would be a weighty argument for a categorical ban on HGGE, as demanded by UNESCO, for example.⁷⁵

Since these problems are not limited to the first generation born out of HGGE but affect all the descendants, a common concern about HGGE is that it generally affects the intergenerational relationship in a profound and, as is claimed, detrimental way.⁷⁶ The reason for this is that editing the germline is not only a matter of changing one specific trait for which parents would be accountable, but they would be equally responsible for all other features that were not changed.⁷⁷ This leads to the reproductive process becoming more than before a process of "(co-)construction"⁷⁸ of the specific composition of the offspring's genome, which brings along a new kind of responsibility.

However, I am not convinced that this must necessarily lead to incurably destroyed or perverted parent-child or, more generally, intergenerational relationships. The argument that if reproduction involves procedures of germline modification, then this must change what it means to have been born in such a way that the offspring can no longer congruently integrate this into their own identity and life story or into the generational context, seems to tacitly presuppose normative premises according to which a morally valuable intergenerational relationship is tied to certain forms of reproduction, which cannot include the alteration of genetic traits in the germ line. Intergenerational relationships are complicated matters, I agree, but it is not impossible for ancestors to take responsibility for their decisions, motives, and intentions and to justify them to their descendants, neither is it impossible for the descendants to take note of these decisions, to see them in their context and next to the then possible alternatives and thus to integrate them into one's own life story and the intergenerational context. I do not claim that this is an easy task and I agree that the conceptual and psychological challenges posed by HGGE may be of a new kind. But I doubt that it can only fail.⁷⁹ This is not an argument that HGGE should be allowed, but an indication that no fundamental argument against it arises from this concern. Nevertheless, weighty question marks remain.

4.3. Hermeneutic vulnerabilities

Finally, some further aspects of moral vulnerability have to be taken into account: The parents' decision for a reproductive procedure involving germline genome editing will

⁷⁵ UN Educational, Scientific and Cultural Organisation (UNESCO), *Universal Declaration on the Human Genome and Human Rights*, 11 November 1997, available at: <https://www.refworld.org/docid/404226144.html> [accessed 10 July 2023].

⁷⁶ Cf., e.g., Jürgen Habermas, *The Future of Human Nature* (Cambridge: Polity Press, 2003), Michael J. Sandel, *The Case Against Perfection: Ethics in the Age of Genetic Engineering* (Cambridge: Harvard University Press, 2007), Christina S. Schües, *Philosophie des Geborenseins* (München: Alber 2016), Rehmann-Sutter, 'Why Germline Editing is More Problematic'.

⁷⁷ Rehmann-Sutter, 'Why Germline Editing is More Problematic', p. 22.

⁷⁸ Rehmann-Sutter, 'Why Germline Editing is More Problematic', p. 20.

⁷⁹ A meaningful concept of interpretation of oneself and one's own coming into being presupposes that the respective interpretation is precisely *an interpretation* and thus *one* attribution of meaning *among other possible* attributions of meaning. Self-interpretations are always contingent, even if this is sometimes difficult to see through from the interpreter's inner perspective. In this respect, it must be conceded that the concrete circumstances of one's own emergence are, in principle, always open to interpretation and reinterpretation.

certainly determine the life of the future child in a fundamental way. One cannot anticipate what it will mean for the child and its self-perception to be brought into the world by means of a germline editing procedure.

As long as HGGE procedures are not established and widely used procedures in reproductive medicine, children born through HGGE procedures can easily become victims of stigmatisation. They could be branded as ‘non-natural’ children or as ‘not fully human’. On the other hand, this could also lead parents to conceal the circumstances of conception. This would amount to a violation of children’s right to know the circumstances of their creation. An analogous situation is that of in vitro conceived children using anonymous donor gametes: in order to protect them, the origin of the gametes is concealed, which can lead to difficult psychological conflicts and strained relationships with the parents for some of them who, later in life, learn about the circumstances of their conception. It is impossible to foresee in what way this would influence the psychological development of the children, but also the relationship between parents and children.

There is, therefore, a significant danger that HGGE can lead to hermeneutic injustices in the individuals affected by it, insofar as they may lack the hermeneutic and conceptual resources to articulate experienced suffering.⁸⁰ We are also hermeneutically vulnerable beings and HGGE would bring a new kind of conceptual and hermeneutical challenges in reconceptualizing intergenerational responsibility and accountability. However, the need to reconceptualize our moral and social vocabulary is a challenge that is not limited to HGGE, but is, to a significant part, tied to the development of individuals and society over time, since, as Kierkegaard once noted: life can only be understood backwards but must be lived forward.⁸¹ Important elements of dealing with challenges of technological developments in a socially responsible way are to cultivate a culture of sensitivity and attention to needs and wants, and to try to anticipate as well as possible the potential implications for individuals and society before allowing them into application, and to take measures to avoid potential vulnerabilities as far as possible.

5. Conclusion

My aim in this paper has been to look at the emerging technology of germline editing from a vulnerability ethics perspective and to explore the extent to which this perspective can be fruitfully applied to the challenges associated with this technology. In doing so, the starting point of the vulnerable subject has proven particularly helpful and fruitful for application in this biomedical context. Liberal conceptions of ethics based on a model of (hypothetical) balancing of interests among contemporaries find it difficult to adequately consider the position of future persons. Here, the approach through a lens of vulnerability offers a helpful supplement without having to give up central aspects of traditional liberal ethics such as the importance of autonomy. Precisely because the perspective on vulnerability does not start from an ideal state of an adult, capable of action, well-informed and autonomous subject, but rather “recognizes that individuals are anchored at each end

⁸⁰ Miranda Fricker, *Epistemic Injustice: Power and the Ethics of Knowing* (Oxford: Oxford University Press, 2007), pp. 147-175.

⁸¹ Kierkegaard, Søren, *Kierkegaard's Journals and Notebooks, Volume 2: Journals EE-KK*, edited by Bruce H. Kirmmse, K. Brian Söderquist, Niels Jørgen Cappelørn, Alastair Hannay, David Kangas, Vanessa Rumble, and George Pattison (Princeton: Princeton University Press, 2015), Journal JJ:167 1843, p. 179.

of their lives by dependency and the absence of capacity"⁸², the beginning of life, which is characterised by radical dependency, and both the vulnerability of the (future) parents and the vulnerability of the (future) children could be taken into account, without making the mistake of considering the latter merely as deficient compared to the ideal state of autonomous adults, but as a phase of life that is to be valued in its own right.

I adopted the taxonomy proposed by Rogers *et al.* to differentiate different layers and aspects of vulnerability and enriched it with the dimension of moral vulnerability. In the application to HGGE it became apparent that all these aspects are important in the evaluation of HGGE in light of vulnerability ethics.

I distinguished various applications of HGGE according to their primary objectives and the method by which these objectives are sought to be achieved roughly into four categories. All of them are based on a claim that HGGE can (and should) be used to reduce vulnerability of some sort. In light of the taxonomy of vulnerability, HGGE applications that aim to enhance individuals by introducing genetic traits into the germline without a direct health benefit, I assumed that they are most often based on a perception of situational vulnerability, and I have argued that it is unacceptable to try to address situational vulnerabilities, which could be responded to with political or social measures, through the use of germline modification techniques. Provided that HGGE could ever be said to be safe and effective, I have argued that only applications aimed at restoring normal physiological functioning, correcting, and preventing health-impairing or even life-threatening genetic conditions, are acceptable objectives of germline modifications, since in these cases, the technique might be a mean to reduce overall vulnerability in future generations.

However, I emphasized that the proviso of safety and effectiveness is a considerable one, since in view of a child born through a procedure of germline editing no additional risk would be morally acceptable. However, as I have tried to show that a particularly neuralgic point seems to lie precisely at this point, which is particularly prominent in the vulnerability perspective: in the bioethical discourse on HGGE, the situation of couples who are carriers of a severe genetic disease is usually constructed as the entry point for the first clinical applications of HGGE, because here the assumed relationship between risks and opportunities is depicted as being in a particularly favorable balance. I have tried to show that this construction is based on a (often tacit) preconceived normative weighting of parental wishes for a genetically own child and the hiding of alternative options (such as IVF&PGT or donor sperm), which, under the guise of empowering affected couples in their reproductive autonomy, tends to bring with it the danger of creating new vulnerabilities: On the side of the future child, whose moral claim to emergence with minimal risks tends to be ignored, and on the side of the parents, whose situation threatens to become a means to the end of establishing HGGE. Both would be consequences that threaten to compromise the moral integrity and dignity of both the future parents and the future child.

Looking at HGGE from a vulnerability perspective could thus demonstrate that the question of possible approval should not only be based on the technical criteria of safety and effectiveness. I discussed several implications of HGGE for the affected parents, children, the relationship between parents and children, intergenerational relationships in general, and for society in light of (some of) the involved vulnerabilities. In doing so, I have supported the view that HGGE would entail a fundamental change in intergenerational

⁸² Fineman, 'The Vulnerable Subject', p. 12.

responsibilities, but at the same time rejected that this can only fail. In addition, the discussion of a new technological development has led us to focus on another dimension of vulnerability: Hermeneutic vulnerability, which in a sense forms the subjective correlate to decisions under uncertainty.

I hope that it has become clear from these considerations that a sufficiently nuanced vulnerability perspective can offer a conceptual tool that is suitable for analyzing the ethical challenges posed by the possibility of germline modifications and – in some questions – also for making an evaluative judgment. Given the uncertainty as to the direction in which developments will proceed, however, uncertainties remain in the ethical judgment even in this perspective, which can probably only be dealt with appropriately in the context of a more intensive, open, and participatory society-wide debate.

It should, however, have become clear that actions aimed at preventing harm and remediating vulnerability may be associated with the risk to “exacerbate existing vulnerabilities or generate new vulnerabilities” and generate “pathogenic vulnerabilities”⁸³. As we move forward in exploring the possibilities by manipulating the genome and developing new applications, we should be concerned that our pursuit is not guided by the fiction that it is a goal in itself to erase vulnerability. “Vulnerability can never be eliminated since otherwise humanity itself would be erased.”⁸⁴ And this should never be neither the aim nor a side effect of any technical innovation.

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⁸³ *Ibid.*

⁸⁴ ten Have, *Vulnerability*, p. 129.

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