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Why Human Germline Editing is More Problematic than Selecting Between Embryos: Ethically Considering Intergenerational Relationships

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Do we have a moral obligation to genetically cure embryos rather than selecting between them? Such an obligation would be an ethical argument for human germline gene editing (hGGE) to avoid the inheritance of genetic conditions instead of using pre-implantation genetic diagnosis (PGD). In this article, the intuition that we do have such a moral obligation is critically evaluated. The article first develops a theoretical framework for discussing the ethical questions of hGGE. This framework is based on an exploration of the phenomenology of the germline, from both biological and philosophical points of view. It interprets the germline as an embodied intergenerational relationship that carries meanings for the parents and for the children-to-be. It relates them to previous family generations, and to their own children. Hence, the germline is a phenomenologically much richer concept than just the line of cells that carry the inheritable genetic information. Against this background, selection is compared with editing and a key moral difference is identified: editing is in effect an act of co-constructing the genome, which necessarily assumes a wider range of responsibilities that include those parts that are left unedited. Introducing hGGE into societies would hence significantly affect and change the moral structure of the intergenerational relationships. Selective implantation, on the other hand (in the context of PGD), is based on a moral choice in favour of the embryo which is to be unaffected by a disease or disability that causes suffering, rather than selecting knowingly the affected one. The claim that hGGE is in the best interests of the child-to-be counterfactually assumes the presence of a patient who has an interest in being cured. The embryo (a potential future patient) is, however, brought into existence by the same act that is also the treatment. The future children who would result from treatment by hGGE may rather

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have an interest in *not* having been treated by hGGE, since it makes the intergenerational relationships more complicated and burdensome. The question 'Is hGGE justified, or even an obligation?' is answered with a No.

KEYWORDS germline, gene therapy, germline gene editing, phenomenology of reproductive genetics, intergenerational relationships

1. Introduction

The technology of purposeful DNA modification has advanced rapidly in the last few years with the development of RNA-guided endonucleases such as the CRISPR-Cas9 system. What was practically inconceivable – modifying just one detail in the whole DNA sequence of an organism in a near perfect way, and without causing serious side effects (off-target mutations and other unwanted effects) – has now come within reach. The obvious lack of safety at the present time is no longer a convincing ethical argument for rejecting human germline gene editing (hGGE) *in principle*. It is only an argument *for the present time*. This has been recognized by highly ranked regulatory advisory boards (National Academies 2017). The question needs to be clarified: *Once it is safe enough, why should it not be done?* Safety is, however, an issue at the present time; I will say a couple of things about this in Section 4.

But let us start with the 'safe enough scenario'. Since it cures the embryo, hGGE would be able to claim a moral advantage over selective procedures: it repairs the germline of an affected embryo rather than screens it out. Many share the intuition that curing is better than selecting. Cavaliere (2017) makes this point. In most medical contexts it is justified. However, whether it also applies to the special circumstances of hGGE is unclear, since the same act (IVF plus hGGE), which intends to cure the embryo, at the same time creates it. There was no needy patient before. One of the main reasons behind the intuition that curing is better than selecting is that selection consists in deciding which of the embryos should be implanted and which will be discarded. Pre-implantation genetic diagnosis (PGD), which is an option that enables some couples with an inheritable condition to avoid a tentative pregnancy (Rothman 1986) and possibly an abortion, inevitably produces embryos to be abandoned.

2. The best interest claim in hGGE for therapeutic purposes

An act of curing presupposes (i) a person who is ill and will be better off after and (ii) an individual who can live well or unwell. Both assumptions are questionable in the case of the pre-implantation embryo. Presumably, there *will* be a person in the future who will have benefitted from the cure, once the child is born. This is the *therapeutic assumption of hGGE*. It aims at producing a future well person, not a patient in need. Apart from the hope that the treated embryo will in fact be born and develop into a healthy child, the therapeutic assumption rests on the premise

(iii) that this person-to-be will have an interest in having been genetically altered, in order to be cured. Without assuming that the cure is *in the best interests* of the future patients, it cannot be seen as a cure. Otherwise, it would just be interference, which is in the best case indifferent in value terms, or perhaps even a nuisance or a harm, but certainly no cure. To qualify as a 'cure', the patients' perspectives (anticipated and future real) cannot be disregarded. I shall call this assumption the 'best interest claim'. To assume that hGGE is in the future patient's best interest is necessary to justify hGGE under a therapeutic objective. The therapeutic assumption and the best interest claim are hence closely related.

The implications of the best interest claim for the ethical evaluation of hGGE need to be better understood. Tackling this is the main task of the present article. Without careful clarification, we are poorly equipped to decide whether hGGE should be accepted or rejected, and we cannot decide ethically about germline therapies. The argument is basically this: if the best interest claim in the therapeutic assumption of hGGE is rejected, the project of hGGE loses its therapeutic justification.

Apart from the therapeutic justification there might, however, be other ways to justify hGGE, for example, that it can lead to an improvement of the genetic conditions of future generations by making them stronger or more capable in certain respects. This would however then be an ethical justification as genetic enhancement, not as therapy. Here, I will not ponder the complexity of ethically arguing for or against enhancement or the ambiguities of its distinction from therapy (Scully and Rehmann-Sutter 2001). I just want to mention that enhancement also rests on a best interest claim, although a different one, namely (iv) that this person will have an interest in having been genetically altered, in order to be 'enhanced'. Enhancement, as Harris (2007) has stressed, implies that the intervention is good for the person who receives it. Otherwise, it would not, properly speaking, be an enhancement.

In order to evaluate best interests claims such as (iii) and (iv), we need to adopt a perspective from the point of view of those who will be affected by hGGE manipulations: the future patients. Patients of hGGE are special in at least two ways, since they are not patients in a traditional sense. First, they have not been ill before the treatment; the cure happens either on germ cells before fertilization, or in the context of the assisted reproductive treatment that brings them into existence. As Giulia Cavaliere points out, if applied to a pre-implantation human embryo, hGGE can therefore only be 'pre-emptively therapeutic' (2017, p. 5), since there is no person to be treated at the moment the technology is applied. This affects the structure of the therapeutic imperative in this relationship, i.e. it results in a lack of moral obligation to treat vis-à-vis any existing pre-implantation embryo. An obligation to treat would only emerge in the future from the potential suffering of the child to be born. Second, hGGE changes something in the parent–child relationship, i.e. what it means to be born from somebody (Schües 2016, 2017). Therefore, bioethics needs also to consider the intergenerational relationships of hGGE patients with those living before and after them and with those other people whose genomes remain unchanged, who will live together with them in families and society.

In order to answer the ethical question raised by the possibility of hGGE, we need a more contextualized concept of the germline as a *corporeal intergenerational nexus*. In such a theoretical framework, the existential, social and ethical significance of the germline need to be understood. Biology cannot tell us this, since it is not hospitable to existential and social meanings. Here I shall sketch out a proposal for such a theoretical framework, which is thoroughly grounded in biology but incorporates the phenomenology and hermeneutics of intergenerational family relationships.

3. Theoretical framework: the germline as intergenerational relationship

3.1. Biology of the germline

The background for discussing questions about the existential and social meanings of germline editing is biological knowledge. We need to check the relevant aspects. Looking more closely at the state of research on the germline surprises those who have in mind the popular picture of the germline as an uninterrupted lineage reaching from the zygote to the germ cells, and then to a zygote and to germ cells and so forth, and depicts the bodies of the individuals (the mortal 'soma') as outgrowths, which, in popular representations of 'Weismannism', stand on the baseline that represents the continuous germ plasm (e.g. Hardy 1965, p. 76). This picture invites an essentialist reading of the germline as the bearer of a 'master genome' of the organisms.

Current biological research takes into consideration the relevant contexts, and thinks in systems. The lineage that we call germline can only come into existence within the cell–cell relations making up the organism within its surroundings. In mammals, we know that primordial germ cells – the precursors of sperm and eggs – originate from the postimplantation epiblast cells during embryonic days approx. 6.5–7.5 (Magnúsdóttir and Surani 2014). Before that, embryonic stem cells are not yet differentiated into germline cells. Primordial germ cells are distinguished by their specific cellular morphology and high-level expression of alkaline phosphatase (Samuels and Friedman 2015, referring to earlier literature). The emergence of germline cells therefore, contrary to the still popular image, involves differentiation and should be seen as an achievement of the cell–cell interactions in a multicellular organism.

Differentiation during the correct development of primordial germ cells, and later of the germ cells, involves complex processes of epigenetic erasure and reprogramming, induced by cell–cell interactions in the developing multicellular system (Stringer *et al.* 2013). During these processes, the germline lineage is a *product* rather than the origin of the early organism. Furthermore, the studies of genetic mosaics show that simultaneous mosaicism occurs in both the germline and the soma and that the germline surprisingly cannot be strictly clonal (i.e. arising from one single ancestral cell) but arises from at least two, and possibly multiple, cells in the embryo with different ancestries (Samuels and Friedman 2015). The process of primordial stem cell development in the human embryo, however, is not yet fully understood.

The phenomenon of a 'germline' was first reported in the 1890s by August Weismann, who discovered the existence of a line of specialized cells with the potential to regenerate another similar animal in a potentially immortal fashion. At that time, Weismann could not know about the molecular mechanisms of cell differentiation; he observed how the cells divide and differentiate phenotypically. Weismann established that, in many metazoa, germline cells develop separately from the somatic cells, which are destined to die in one generation. He had studied several organisms, such as *Pandorina morum*, a simple organism in which all cells have the potential to regenerate another animal and hence no germline exists, *Volvox minor*, where germline cells can be distinguished from somatic cells, and – already much more complex – the worm *Ascaris nigrovenosa*, where he described a precise embryonic cell lineage after the first division of the zygote (Weismann 1892, p. 258). In *Ascaris*, the primordial germ cell (Weismann's term was 'Urkeimzelle') appears only after cell division 8. In humans, we know that during *in vitro* development of embryos, on average five cell divisions have taken place by day 6, before primordial stem cells are present (Herbert *et al.* 1995).

Human primordial stem cells appear only after multiple cell divisions that include differentiation, epigenetic erasure (a kind of 'forgetting' within the epigenetic memory system) and epigenetic reprogramming within a dual somatic environment, which consists of both the embryonic system and – during *in vivo* development – the wider context of the female reproductive organs. The germline, surprisingly, is *not the origin of the soma* but itself *a result of complex somatic interactions* between early embryonic and somatic cells that lead to the distinct epigenetic changes and particular morphology and behaviour of primordial germ cells. The germline that links the generations is therefore not a direct cell line leading from germ cells to the zygote to new germline cells. It leads literally *through the body* and the cells that are capable of starting a new round of germline are the product of an intercellular interactive process that occurs in each generation.

For the task of philosophical interpretation of human reproduction, it is important to note that the germline cells' capacity to originate a new generation is not inherent in a particular cell lineage, but something that *emerges* in the context of other cell lineages. We should not think of it as a capacity that derives directly from the originating capacity of the zygote. The origin of the originating capacity of the germline cells is an accomplishment of the embryo as a multicellular body. Therefore, the germline must be formed by the developmental system of the body like an organ of the body. It is a part of the body with a specialized function and meaning. Its formation starts very early in embryonic development, as a result of a set of complex *somatic* processes that involve cellular interactions, epigenetic erasure and reprogramming. If this process of germline development did not work accurately, there could be literally no further generations. Evolution and reproduction of the species relies on it. Without a functioning germline, our species is doomed to extinction.

This has two obvious implications. (i) It is really difficult to defend a view that the germline should be spared from intervention because it has the metaphysical status of an organizer of the developing organism. This would be an essentialist

interpretation that is not based in biological knowledge.[1] Therefore I reject the view that the germline is inviolable *because* of its special biological significance. We need a refined philosophical concept of the germline that avoids what one could call 'germline essentialism'. (ii) On the other hand, the reproduction of the germline, however only partially understood, is a delicate and vulnerable process that has a crucial function for the species.

3.2. Phenomenology of the germline

By 'phenomenology' I mean a philosophical methodology that systematically considers lived experience. Phenomenology looks at *how* things are experienced, i.e. how they are *given* to us as subjects of perception, thought and action, in our lived experience (Moran 2000; Carel 2011). We might therefore ask: how is knowledge about the germline given to us in experience? What significance does this embodied knowledge have for our life?

This way, the germline can be seen as a relationship that links the generations and has its lived reality in families. The cellular lineage of the 'germline' represents the physical reality of this intergenerational relationship. Reproductive cells both exert a biological role and have a social significance in the context of the link between generations. Of course, there are other levels of intergenerational relationships, which have little to do with cells and genes but are also important – such as family traditions, architecture, arts and habits (culture), societal structure or the alteration of ecological environments. But among all these levels, the germline is perhaps the most intimate and corporeal, since it is 'genetically' linked to the shape, structure and functional capabilities of our bodies. Moreover, the link is 'generative' (Schües 2016, chs. 4 and 5) in the sense that alterations within the composition of germline cells will alter the shape, structure and functional capabilities of the bodies of the generations to come, for better or worse, and in the worst case, such generations cannot continue to be successfully generated.

We cannot directly experience the human germline, but we *know* about the germline and have ideas about and experiences of its effects in the context of familial relationships. However, we do not see or feel germline cells in our bodies, in the same way we feel our heart beating or back aching. Sperm may be sometimes visible during sexual activity, but sperm and egg cells themselves play a hidden role when a pregnancy starts. Nevertheless, in our everyday lifeworld (Schütz and Luckmann 1979) and in the familial and more generally the intergenerational relationships, the germline also exists *as* knowledge (or partial knowledge). We *know* that we have inherited things, and we have ideas (also stories and phantasies) about how this works. And we know that our genomes will become important for our future children. This knowledge directly and indirectly poses interpretative questions. What do the genomes and the germlines mean for us? How do we integrate what we know about genomes and the germline into the contemporary social relationships and the social relationships that connect different human generations

[1] See the related criticism on essentialist interpretations of genes and the genome in the context of developmental systems in Neumann-Held and Rehmann-Sutter (2006), Oyama (2000) and Griffiths and Stotz (2013).

in time backwards and forwards, both in families and in wider societies? And what challenges arise from it?

Our ancestors are genetically linked to our lived bodies precisely *via this line of cells*. They are linked to our lived bodies in many other ways too, but genetics plays a crucial role in the health and functioning of the body that we live. The germline reaches far back in evolutionary time: first down the family tree, and then linking us with those forms of life that existed before the primates branched out. And it reaches forwards in time to an as-yet-unknown future of our kind. It is therefore in family and evolutionary intergenerational relationships reaching backward and forwards that germline alterations acquire moral significance. This is the context in which the ethical implications of hGGE must be understood and also evaluated.

Looking at the most comprehensive currently available background documents, such as the 2017 report of the U.S. National Academies of Sciences, Engineering and Medicine, the germline is only seen as equivalent to heritability. '[G]ermline editing is highly contentious precisely because the resulting genetic changes would be inherited by the next generation, and the technology, therefore, would cross a line many have viewed as ethically inviolable' (National Academies 2017, p. 20). This implies a rather limited picture of the intergenerational relationship, insofar as it depicts the relationship as going only in one direction, into the future. The view backwards is neither mentioned nor reflected upon. It is important to keep in mind that the view backwards works in two ways: (i) from the future generations to the earlier generations (or from us, the present generation, to our ancestors) and (ii) the view in a 'future perfect tense' – from the present generations to the future, anticipating their view on the earlier generations. The intergenerational relationship, like every relationship, has components that are directed in both ways. This corresponds to Schües' general description of generative intergenerational relationships as being born 'by somebody with somebody', including both temporal and interpersonal aspects (2016, ch. 5).

Family relationships are conceptualized as relationships of care and responsibility. Both concepts reach backward and forward in time. They morally relate older people to younger ones, and younger with older (Finch and Mason 1993, Kittay 1999, Alanen 2014). The question of how to handle the germline genetically, including whether we do gene editing and how we do it, therefore becomes part of the meanings these relationships have for us and for those living in the future. The ethical significance of practical knowledge about the germline, about its functioning, its fragility and about the possibilities of manipulating it, therefore need to be tackled in the context of these moral responsibilities and the inherent accountability of these relationships.

This phenomenological perspective on the intergenerational relationship is, I argue, of key importance as a component of the theoretical framework for an accurate ethical discussion about hGGE, no less important than risks and benefits, well-being and children's rights. A series of questions can be raised and better clarified on this basis. Here we will discuss only two of them: how should we deal with biological safety issues related to hGGE between generations? And how would relationships be affected by hGGE, in comparison with the effects of selective interventions such as

PGD or prenatal diagnosis? Other questions can also be investigated, for instance: is the claim that there is a moral responsibility to produce children with optimal genetic starting conditions (discussed under the title of 'procreative beneficence' by Savulescu and Kahane 2009) itself based on certain assumptions about the moral structure and meanings of these relationships? How do germline technologies, as part of biomedicine, affect other types of relationships in society and the human condition?

4. Safety reconsidered

At the present moment, based on the available evidence about the incidence of off-target mutations caused by CRISPR-Cas9 interventions, hGGE is not considered safe enough to be applied clinically (National Academies 2017; Ormond *et al.* 2017). However, research is progressing. In this situation, the critical question about safety is not: when is hGGE safe enough? but rather: *how can we know* when it is safe enough? This relates to study designs: how should the relevant data be collected, and the relevant studies be done? What are the criteria for responsively evaluating available data on safety?

I doubt that we know all we should know about safety, before doing it and collecting 1:1 experience in real life, over a few generations. A longitudinal study involving several generations, which would provide evidence about possible late-onset side effects that appear only in the subsequent generation, will realistically be conceivable only as a measure of monitoring after approval of the treatment. They are however ethically problematic because children are involved in the study without their consent and because such monitoring might be experienced by the families as intrusion.[2] For trials involving the first attempts to treat to be feasible they will probably be much shorter and less conclusive.

Safety should therefore not be seen as a black-or-white issue. Safety has shades of uncertainty reaching from (i) certainly unsafe to (ii) more or less unsafe to (iii) ideally safe. Today we are at stage i. Probably, the best we can realistically expect is to arrive at a stage where the uncertainties are sufficiently low to merge into the background of what is normally uncertain in human reproduction and must be accepted anyway. This requirement will have some similarities to the 'minimal risk' requirement in clinical trials in vulnerable groups (Lantos *et al.* 2015), since it compares the added risk to something that is usually accepted, or is inevitable, and then argues: if we accept this level of uncertainty anyway, why should a beneficial new technology be halted?

There is one key issue to be mentioned: according to the National Academies' recommendations, an hGGE intervention will first become acceptable 'for compelling purposes of treating or preventing serious disease or disabilities' (National Academies 2017, p. 10). How should this be relevant? If we take that seriously, it seems that there will be a temptation to allow a treatment for a serious disease or disability even at the stage of a higher residual risk than interventions into healthy embryos

[2] The intrusion argument was put forward by Nancy King at the Human Genome Editing conference in Belgrade, August 2017.

would demand. The argument would then be made that the affected individual will benefit if serious disease or disability is prevented or treated, at the cost of a risk of a side effect that is considerably less harmful than the disease or disability. Similar considerations are relevant in clinical decision-making about treatment of serious diseases. A cancer patient, for example, has good reasons to accept a considerably higher risk and burden of a potentially life-saving treatment than a patient with a cough.

However, this argument, if it is made in the context of hGGE for serious diseases, is not sound. This child-to-be-born will only be born because the treatment took place. Seen from the future child's perspective, the side effects of hGGE treatment cannot be justified through comparison with the potential for living with disease or disability, which is prevented. Hence, for the child who is hopefully healthy, no higher risk is acceptable than for all healthy children who are included in clinical trials, i.e. only 'minimal risk' (Lantos *et al.* 2015).

Comparison with non-existence does not help either. It would be unfair to ask of a child to accept risks or harms by suggesting: you are supposed to accept it because otherwise you would not exist. This assumes an impossible comparison. The option of 'otherwise not existing' is just not conceivable to the child. Such a comparison is illicit.

We are in a situation that existentialist philosopher Simone de Beauvoir aptly described as follows: 'The means, it is said, will be justified by the end; but it is the means which define it, and if it is contradicted at the moment that it is set up, the whole enterprise sinks into absurdity' (De Beauvoir 2015, p. 134). This can be explained as follows: we are misguided if we try to justify the risk of side effects of hGGE by the end it serves, i.e. by the disease or disability that is to be prevented. The means define the end: the intervention of hGGE defines the children-to-be-born as its outcome. And if the aim of producing healthy children is compromised at the moment the project is set up, i.e. at the moment the hGGE intervention is planned, with all that belongs to it, IVF and everything, then the whole enterprise of improving human reproductive capabilities with germline interventions sinks into absurdity. This logic of risk and responsibility seems compelling when we consider the (hypothetical) perspective of future children who will be born with an edited germline and ethically evaluate what has been contributed to their existence by a past hGGE intervention that might have been hasty and inadequately safe.

5. The moral difference between selection and editing

In a comprehensive review of the ethical issues of hGGE, the British Nuffield Council 2016 affirms that

> [s]imply knowing that there is a significant risk of a serious, well-characterized genetic condition […] would not make genome editing an obvious reproductive option. Where there is a known risk of genetic disease with a well-characterized genetic basis, it is often possible to exclude affected embryos after preimplantation genetic diagnosis. (Nuffield Council on Bioethics 2016, 4.31)

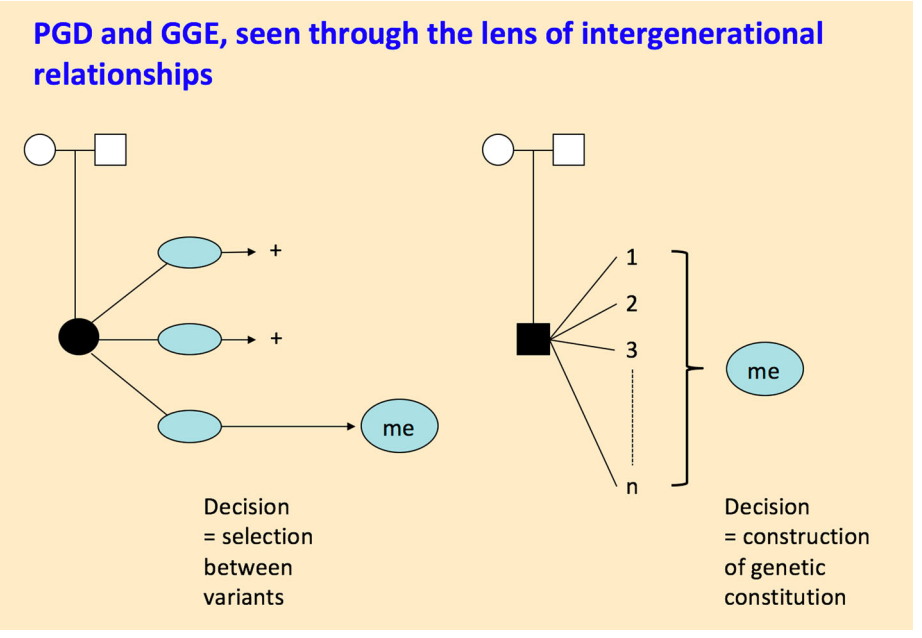

FIGURE 1. PGD and hGGE seen through the lens of intergenerational relationships and compared with regard to moral implications (see text for explanations).

There are, however, rare exceptional cases where PGD will not work. They include defects in the Y chromosome, couples with a dominant genetic disease (such as Huntington's or breast cancer) where one parent is homozygous (100% risk for offspring), recessive genetic disease where both parents are homozygous (100% risk), or cases where there are just no suitable unaffected embryos for transfer (Nuffield Council on Bioethics 2016).

The underlying idea of this comparison is either that if PGD is available, a more ethically controversial and medically less safe intervention such as hGGE is *not necessary*, or even impermissible; or, on the other hand, the idea is that, given the broad acceptance of PGD, hGGE must be acceptable as well since it leads to the same effect, namely an embryo unaffected by the disease-producing mutation. Even more so, because hGGE treats the embryo rather than just selecting it.

I see a more fundamental difficulty here. Considered as acts in the context of intergenerational relationships, selection and editing (PGD and hGGE) differ from each other in key respects. Selection is a different act from editing, with different moral implications for the existence of the child-to-be. This can be seen when regarding it in the future-past-tense perspective, i.e. from the hypothetical perspective of future children (see above Section 3, and Figure 1).

Let us assume the future child is in the position of 'me'. In one situation, 'me' is born after PGD, in the other, after hGGE. Let us further assume the future child is old enough to understand and be informed about the parents' actions that have

led to her or his birth.[3] In the first case, 'me' knows that before pregnancy, one or more 'sibling' embryos might have existed which have not been chosen for pregnancy. The parents have been, as 'me' can well imagine, trying to avoid harm to the future child. After IVF and PGD, they had to choose between the embryo(s) that were diagnosed with a harmful genetic condition, and 'me' who did not have that genetic condition. At that moment, the parents were in a situation in which they arguably saw a moral reason for choosing the unaffected rather than the affected embryo. Durand (2017) has called this the 'principle of procreative non-maleficence'. It states that in a situation of choice parents should, for good moral reasons, select the embryo that has no harmful or a less harmful genetic conditions. If they did not do so, i.e. if they deliberately chose the embryo affected by a harmful genetic condition, they would act against an ideal of good parenting. This argument by Durand, however, assumes that the situation of choice is given. I cannot see how it could support a duty to produce or enter this situation of selection, i.e. of *performing* PGD in the first place. The argument takes PGD as a given and only applies to the act of selection after PGD is performed. The decision to do PGD (or prenatal diagnosis) or to abstain from it has completely different moral implications, which we cannot discuss here.[4]

If parents – for preventive reasons, i.e. to avoid their child suffering from a severe genetic disease – have chosen to perform PGD and are in the situation of choosing, as Figure 1 suggests, then this choice does not affect the body of the child resulting from the pregnancy. The only implication is that other potential siblings have not been born, and some of them would probably have been affected by this harmful genetic condition.

If seen from the child's perspective, this knowledge could be a topic of discussion between parents and child, but it does not affect this relationship in a fundamentally negative or harmful way. If the child would think that she or he has only been born because of fulfilling a criterion, and therefore feels not accepted unconditionally, parents could explain their intentions, and the child might be able to understand it. Under this perspective, the choice the parents made is comparable to abstaining from getting pregnant at a time where there would be a high risk of harmful influences, such as when being under special drug treatments. This is also a situation in which 'me' would only be born because the parents decided as they did, being aware of their parental responsibility for the health of their future child.

The situation is, however, significantly different in the second case, in which the parents have undergone hGGE treatment to have a child with an edited genome. Let us again assume that 'me' has been told about the parents' acts, decisions and considerations. So 'me' knows that mutation x of a whole series of potentially harmful or risk-contributing mutations (1, 2, … *n*) has been edited. Or, let us say, two or three edited mutations. Parents, together with their genetic counsellor, have chosen x, x and y, or x, y and z. The resulting genome that is embodied by 'me' is based on these decisions, in part parental, in part technical, in part

[3] The symbolized genders of the two *me*s on the two sides of the graph are arbitrary.
[4] On prenatal diagnosis Gregg (1995), Rapp (1999), Haidar *et al.* (2016); on PGD Rehmann-Sutter (2017).

societal, that defined which mutations should be edited and which should not (or cannot) be edited. It is therefore impossible to decide which mutation should be edited without simultaneously becoming responsible *for what is left unedited*.[5] Why did the parents not fix the other genetic flaws that could have been edited in the same run? This is less easy to answer, if the child asks, given that we all carry a potentially high number of more or less problematic mutations. Hence, 'me' in the case of hGGE is looking at a different kind of decision made by her or his parents (or their predecessors). It is not a choice among given variants but a (*co-*)*construction* of a variant. If the genome has social meanings in the context of intergenerational relationships as well (which we assume here), these meanings differ considerably.

After hGGE, the genome of the next generation (and their progeny) is never just 'given', but is always the result of certain editing rules and editing decisions. It contains agency, and this affects the parenting relationship. It establishes a different kind of relationship between the generations. The composition of the genome has been decided about; it is made by people. Future generations cannot start from a genetic base that is composed of the parents' body cells and chance, uninfluenced by the medical decision-making of their predecessors. We could put this in more dramatic words: the genome will no longer be innocent. Responsibilities of a new kind would therefore enter the moral structure of intergenerational relationships.

I am aware that pregnancy has never been free from health-related responsibilities, for example, avoiding toxic drugs. My argument is not that responsibility will be generated where no responsibility was before. From a societal perspective, however, parental responsibility and accountability will change with hGGE. I can see no reasons to assume that these changes are beneficial. They will not contribute to the well-being and good life of future societies. — For the same 'moral' reasons, the introduction of hGGE could not stop after only a few edits but lead to more and more edits. Everybody could be treated for genetic risk factors. The process cannot be consistently stopped by sound reasons and endpoints.[6]

An additional but different problem is justice. If we realistically assume that only a small and wealthy part of humanity will have access to hGGE technology, the generations to follow will experience a biological split in the human population between those who have been edited, or have inherited edits from their parents, and others who have not. This might pose further challenges to solidarity (Prainsack and Buyx 2017) between the edited and the non-edited, or vice versa.

I see reasons to believe that something *will* change in societies and in the transversal (longitudinal) aspects of generative relationships. Before humanity rushes into practising hGGE, driven by competitive and ambitious researchers, institutes, or even nations who want to be the first, or driven by the appeal of scientific progress and the apparent moral superiority of curing over selecting, we should be clearer about *what it will change*, and what we consider essential for a good life in this regard. — It has not escaped my attention that all these issues are, in a fundamental philosophical sense, political.

[5] I have suggested this point already in an earlier article about the ethics of germline therapy (Rehmann-Sutter, 1991), anticipating a situation as we see it now with the CRISPR systems.
[6] This is not a classical slippery slope argument but a realistic projection.

6. What does this argument distinguish?

The difference between editing and selection, one being essentially a construction of new variants, while the other is a choice between existing, unaltered variants, applies to all purposeful changes introduced into the germline DNA, irrespective of whether they are restorative, therapeutic or enhancing. It therefore questions the best-interest claim and also applies to attempts to improve human bodies.[7] A clear demarcation between *therapeutic and enhancing* interventions into the sequence of DNA is difficult, morally ambiguous – and, as we have suggested elsewhere, not without unpleasant socio-political side effects, since it necessarily refers to a standard of normality, which is for good reasons objectionable from a disability bioethics point of view (Scully and Rehmann-Sutter 2001).

The argument does, however, clearly distinguish DNA editing from mitochondrial replacement therapy. This might be unexpected, given the claim that mitochondrial replacement therapies conceptually and legally pave the way for germline interventions (see references in Castro 2016). With regard to purposeful interventions that prevent some mutations in the germline (and not others), the replacement of defective mitochondria by donated 'healthy' mitochondria is not comparable to hGGE. Mitochondrial replacement therapy is repaired with donated (given and unmodified) mitochondria. It is, seen under this perspective, more readily comparable with transplantation medicine than with hGGE.

The distinction between germline and somatic cell DNA editing is clear-cut, as long as we talk about intentional interventions that are brought about by planned genetic interventions. Accidental changes both in the sequence of the DNA and the epigenetic structure of germline cells do, however, occur quite frequently, or could in some instances also occur inadvertently, if genome editing is applied to somatic cells. Ethically, this is a different issue that needs to be further discussed (see Rehmann-Sutter 1991, 2003).

7. Conclusions

We have tackled the question whether hGGE can be, in the best sense of the term, a therapy. In order to resolve this, we have discussed whether the best interest claim of hGGE is justified. We said at the outset that if it is rejected, the project of hGGE loses its therapeutic justification. The result can be summarized with two claims: first, the best interest claim counterfactually assumes the presence of the patient who has an interest in being cured. The embryo (i.e. the future patient) is brought into existence by the same act that is also the treatment. Second, the future children who are brought into being by hGGE can have an interest in *not* having been treated by hGGE, since it makes the intergenerational relationships more complicated and burdensome. For these reasons, I answer the question, 'Is hGGE justified?' with a No. I do not believe, the intuition that curing the embryo with hGGE is morally better than selecting against it with PGD is ethically defensible.

Up to now, it has not been possible to manipulate the genome of the human germline purposefully. It would be something quite new in the history of humankind, and

[7] On enhancement and disability see Eilers *et al.* (2014).

the decision to do so should therefore be considered with utmost caution. The lineage of cells that we call 'germline' can be understood as a corporeal intergenerational relationship that connects us with future and past generations. This relationship is biologically and socially generative, insofar as it enables parenthood in this and subsequent generations. Like its biology is an achievement of early embryonic development (not a given), also the moral structure of intergenerational relationships is an achievement of societies. We know that future generations could not biologically emerge without the germline. How they should be positioned to previous generations is a topic for an ethics of care. I have argued that the relationship is directed to the future and as well to the past. It links future generations genetically and morally back to earlier ones. Insofar as choice and agency are involved, responsibilities and liabilities are emerging. Intergenerational relationships contain many more layers than cell lineages with inheritable DNA. These layers encompass both corporeal and practical bonds: conception, pregnancy, birth and family life.

My point is, in short, that any purposeful introduction of a change into the genome of the germline by hGGE cannot be evaluated purely on the basis of the effects the change itself has on subsequent generations. Changing the germline changes something more basic: it puts the whole set of both potentially harmful and potentially beneficial genes (including all the unchanged variants) *at our disposal*. Editing the germline is, therefore, always more than the edit that is actually performed. It would automatically define what is left un-edited. Unchanged parts of the germline DNA, as well as the remaining risks and side-effects, would then be based on decisions taken in earlier generations, which are, like all decisions, contestable and prone to fallibility. This moral context of the decisions about hGGE would therefore change the moral structure of the relationship between generations in a fundamental and significant way; it would affect the life of new generations in relation to their parents and predecessor generations.

This argument says that we should be careful and act with cautiousness. hGGE would be a social experiment of immense dimensions – probably a poorly planned one. The alternatives (PGD, or if that is impossible, sperm or egg donation) should be considered and comparatively evaluated. The argument of intergenerational relationships that I have proposed here brings one more weight to bear against the assumed health benefits of hGGE interventions compared to doing nothing. There are alternatives without these problematic implications, such as PGD and the donation of germ cells; these are also not without ethical challenges, but do not have the same difficulties. The intuition that we share a moral obligation to cure embryos with hGGE rather than selecting them by using PGD cannot hold up against criticism.

Many share the intuition that hGGE is ethically more complicated than the conventional curing of diseases. I hope it has become clearer why this is so and how this difference can be explained. The change in the living conditions of the descendants and of potentially infinite generations could be well-intended and tentatively justified by an anticipated health benefit of those directly and indirectly affected by it, even though it is impossible for them to consent freely to the intervention in advance. But, as I have argued, this rests on too limited

a view. There is no therapeutic imperative that would justify hGGE, or even make it a moral obligation.

The distinctive feature of hGGE (and its ethically problematic aspect) is *not*, as has been suggested, for instance, by Collins (Collins 2015; critically see Harris 2015), that children cannot consent to the treatment. If we asked for patients to give informed consent, a large part of paediatric medicine would be automatically illegitimate; certainly all of neonatology. The ethics of paediatric medicine always works with proxy consent, with assent of the child as far as possible, according to age and maturity, and with the child's long-term best interests. The distinctive feature of hGGE is rather that there is no individual before treatment in whose best interests it could be to be treated. There is no young child-to-be who has an interest in being cured and in whose best interests parents should act. The individual embryo is produced only in the course of the very treatment that consists of a plan involving 'IVF plus hGGE plus pregnancy'. The treatment in question brings into existence the patient it plans to treat. The assumption that the treatment is in the best interests of the child must therefore be discussed in the perspective of a future past: it will be (or will not be) in the best interests of the individual to *have been* treated by hGGE. We can call the pattern of justification that is in use here a *hypothetically retrospective best interest evaluation*. It involves many more dimensions than just the health outcome.

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