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Risks and benefits of human germline genome editing: An ethical analysis

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Abstract

With the arrival of new methods of genome editing, especially CRISPR/Cas 9, new perspectives on germline interventions have arisen. Supporters of germ line genome editing (GGE) claim that the procedure could be used as a means of disease prevention. As a possible life-saving therapy, it provides benefits that outweigh its risks. Opponents of GGE claim that the medical and societal risks, especially the use of GGE for genetic enhancement, are too high. In our paper, we analyze the risks and benefits of GGE. We show that the medical risk on an individual level might be reduced by further research in the near future so that they may be outweighed by the benefits. We also show that the societal risks of the procedure, i.e. genetic enhancement, are manageable by establishing a regulative framework before the GGE is implemented. Since the effects of modifying genes for the genepool of a given population are extremely difficult to model, the medical risks on the population level might be too high.

Keywords: Bioethics, CRISPR/Cas9, Disease prevention, Genome editing, Germ cells, Germline therapy

Introduction

For decades, potential interventions in the human germline for clinical purposes have been regarded as ethically impermissible. Recently, this strict view has come under review. With the arrival of new methods of genome editing, especially CRISPR/Cas 9, new perspectives on germline interventions have arisen. In their report *Human Genome Editing: Science, Ethics, and Governance,* the American National Academies of Science, Engineering, and Medicine have stated that clinical research using germline genome editing (GGE) in humans should be permitted (The National Academies 2017). In the long run, this may lead to the development of clinical applications. The Academies propose to limit GGE to severe cases of disease and disability where no alternative treatment is possible. It follows that although there are certain contexts where GGE could be used in a beneficial way, it should be used within narrow limits and with caution. GGE is mainly discussed in the context of disease prevention and infertility treatment (Ishii 2017a, b; Long et al. 2014). Disease prevention is widely seen as a benefit that outweighs severe risks connected to GGE. Some even claim the preventative use of GGE to be a moral imperative; its application is an obligation for the sake of patients and future generations (Gyngell et al. 2017). In addition, GGE provides new perspectives for infertility patients who have no other option to create offspring that are genetically related to them. But there are also those who state that the medical as well as societal risks are too high, and argue, accordingly, for a full ban (Lanphier et al. 2015). Although there are no clinical applications of GGE available at the moment, it is important to have an intense ethical debate at this early stage in order to be prepared for coming developments, given the speed at which research efforts are now being conducted. A future clinical implementation of GGE needs an ethical framing which provides guidelines for clinicians.

The aim of our paper is to analyze the ethical implications of editing the human germline by using new procedures of genome editing. Editing somatic cells as an application of gene editing technology, and its ethical implications, is not the focus of our analysis. We discuss GGE as a possible clinical application, not as a research technique. Specifically, we attempt to provide an analysis of the risks and benefits that could arise from such an application. Weighing the risks and benefits of new technologies is important, but it is only one aspect of assessing technologies. We do not claim that our analysis is exhaustive or final; broader ethical analysis still needs to be done in order to thoroughly evaluate GGE. Although we focus on risks and benefits, many other aspects need to be taken into consideration, e.g. questions of reproductive autonomy or access to the procedure. Furthermore, questions of research ethics arise, as well as questions concerning regulations of the translational process. We addressed some of these questions elsewhere (Rubeis and Steger 2016). In this paper, we seek to produce a sound ethical evaluation of GGE in terms of its potential risks and benefits. The focus of our analysis is on this question: whether the benefits of GGE really outweigh the risks that are usually ascribed to a germline intervention? Apart from medical risks on the individual level like off-target mutations and genetic mosaicism, and medical risks on the population level, there are also societal risks like genetic enhancement. That means that the nature, aim, and risks of the possible applications have to be

clarified. It has to be clear who benefits from the method and whether this benefit justifies the risks of its application.

Possible applications of GGE

In August 2017, the first therapeutic germline intervention using CRISPR/Cas9 was reported (Ma et al. 2017). A team from Oregon Health & Science University created zygotes by fertilizing healthy oocytes with sperm cells from a carrier of the MYBPC3 mutation. This mutation leads to hypertrophic cardiomyopathy, a heritable heart condition. By using CRISPR/Cas9, the team then corrected the genetic defect in the zygotes which led to the development of viable embryos. The majority of these embryos was mutation-free. Since the intervention in the germline did occur for research purposes, the embryos were not implanted in utero. This research shows that correcting a gene mutation in viable human embryos using genome editing methods is feasible. It confirms results from earlier research on human embryos by two Chinese research groups in 2015 and 2016 (Kang et al. 2016; Liang et al. 2015) and a team at the Francis-Crick-Institute in London (Callaway 2016).

There are various different applications of genome editing in germline therapy, especially by using CRISPR-based methods (Ishii 2017a, b). All elements of the germline, oocytes, sperm cells, and embryos, can be edited. One possibility is the editing of oocytes. The method could be used to correct the mutation in the TUBB8-gene which is known to cause developmental arrest after fertilization. The method can be applied to the oocyte after retrieval. The edited and verified oocyte could then be used for an IVF. Furthermore, sperm cells can be edited through spermatogonial stem cell (SSC) editing. This procedure could be used for treating genetic infertility. By conducting a testicular biopsy, the SSCs can be retrieved and transfected with programmable nucleases. After genetic analysis and verification, the SSCs can be transferred back into the donor's testes. The edited SSCs then trigger the production of mutation-free sperm cells. In order to ensure reproductive success, the resulting sperm cells could be used for in-vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI). Apart from sperm cells and oocytes, genome editing can be applied to zygotes, i.e. fertilized oocytes. This could be a therapeutic option for several monogenetic diseases such as Huntington's disease or β-thalassemia. After fertilization through IVF or ICSI, the zygote can be microinjected with programmable nucleases. The resulting embryo could be tested by using preimplantation genetic diagnosis (PGD) to ensure that there are no off-target-effects. For the PGD, a blastomere biopsy three days post-fertilization or a trophectoderm biopsy four to five days post-fertilization could be used. After testing and verification, the embryo can be transferred in utero.

There are two possible applications discussed at the moment. The first possible application is infertility treatment. Oocyte editing and spermatogonial editing could be an option for patients suffering from

genetic infertility. The second possible application is disease prevention. Also in this context, the editing of oocytes or sperm cells could be a possible application. Additionally, the editing of zygotes may be a way of correcting genetic errors that are likely to cause health problems later on.

The first studies using GGE on human embryos showed that there are severe medical risks (Liang et al. 2015; Kang et al. 2016). These risks are mainly due to off-target effects. Off-target effects occur when DNA double strand breaks are made at the wrong target site. The result is an inaccurate or incomplete editing, causing improper translocations, inversions or large deletions which can lead to point mutations (Ishii 2017b). The latest research shows that off-target effects in human embryos, although still existing, can be minimized (Ma et al. 2017). Also, the occurrence of genetic mosaicism could be diminished to a minimum. Genetic mosaicism is the coexistence of edited cells and wild types, a condition that may lead to severe health conditions (Ishii 2017b). Due to the multifactorial nature of the processes involved, the exact consequences of genetic mosaicism are hard to predict. However, clinical research is only now beginning. A lot of translational research is needed before GGE can be implemented in clinical practice. Although the latest results mean an enormous step forward, there is still a long way to go before these methods are safe enough for clinical application. Apart from the risks for the embryo and future child that is directly affected by GGE, there is another level of risks to consider. Genetic modifications of the human germ-line will be passed on to coming generations. This means that an off-target effect does not only affect one individual, but possibly many future individuals. How exactly off-target effects and genetic mosaicism would manifest in future generations, is almost impossible to predict which makes this risk incalculable. Therefore, a proper risk-assessment has to include coming generations as well.

Risks and benefits of GGE

At the moment, the empirical evidence shows that any clinical application would be too unsafe (Ishii 2017b; Ma et al. 2017). However, with research efforts speeding up, clinical applications might be safe enough in the near future. Ethical evaluation of further implementation of these initiatives, as well as safety concerns in individual cases, is needed. One of these concerns is the effect of GGE on the population level (The National Academies 2017). Since germ cells are altered, the modified genes could be passed on to future generations (Ormond et al. 2017). Thus, the modified genes could spread within the human gene pool with yet unforeseeable consequences. For example, the genetic trait for sickle-cell anaemia also protects its carrier against malaria. Similarly, there may be as yet unknown positive effects to genes ordinarily considered pathogenic. On the other hand, modified genes which appear not to affect its carrier may turn out to be pathogenic over time. This aggravates safety concerns, since not only one individual, but many individuals or whole populations might be affected by possible pathogenic effects of the modified genes. Due to the complexity of gene frequency and microevolution, it is impossible to manage or even predict the impact of modified genes in future generations.

Another topic in the discussion is the specific way in which the human genome is altered through GGE. Some state that GGE implies a new level of interfering with nature that is to be considered as irresponsible. Therefore, the procedure crosses a line that should not be crossed (Lanphier et al. 2015). Others claim that the risk of misuse is too high (Baltimore et al. 2015, Hildt 2016). Apart from disease prevention or infertility treatment, GGE could be used without any medical indication for enhancement purposes. Genetic enhancement is seen by many as societal risk because it could lead to the creation of two classes of humans, the enhanced and the non-enhanced. This would challenge the very ideas of justice and equality which are crucial to modern society. But there are also those that consider the implementation of GGE as ethically justified. Supporters of GGE see benefits of the method in two areas, disease prevention and infertility treatment (Gyngell et al. 2017; Savulescu et al. 2015).

As we have seen, GGE could be used in order to prevent hereditary monogenic disease like Huntington's or β-thalassemia. As in the case of the carrier of the MYBPC3 mutation mentioned above, GGE would allow individuals with certain hereditary diseases to reproduce without passing on the disease. This would mean an immense benefit for individuals with a known genetic risk who want to have children. They could fulfil their wish to have children without the risk of severe health conditions or ailments. So far, couples with genetic risk depend on embryo selection, gamete donation, or adoption. Embryo selection, mostly through PGD, can be applied in certain cases to ensure that a certain genetic trait is not passed on. The method is elaborate, costly and often stressful for patients. It also implies the discarding of embryos with unwanted traits which is ethically questionable. Also, there are cases of dominant late-onset conditions like Huntington's where a selection of embryos by using PGD is not possible. Thus, GGE could be used to prevent offspring from inheriting pathogenic genes.

Apart from disease prevention, GGE is also presented as a potential infertility treatment. One possible application is non-obstructive azoospermia (NOA) in male patients (Vij et al. 2018). For female patients with a 'missense mutation' in the TUBB8 in oocytes, GGE could also be an option (Ishii 2017b). So far, the only option for these patients to create offspring is through gamete donation. When it comes to gamete donation, legal restraints have to be considered apart from the effort and ethical implications. Since gamete donation is legally prohibited in many countries, the treatment is not always available. It furthermore implies that that the resulting child is not genetically related to both of the partners that apply the method. The fact that the genetic material of another individual is used conflicts with the wish for a child that is genetically related to both partners. Also, when it comes to adoption, this issue is to be considered. The wish for a child implies a child that is genetically related to both partners for most couples. Genetic relatedness, however, cannot be provided by adoption. GGE could be a viable alternative to PGD, gamete donation, and adoption. It circumvents the ethical and legal implications of these options by making a healthy genetically-related child a possibility for potential parents. As Gyngell et al. (2017) claim, for some reproduction partners GGE would be the only option to create offspring

that is genetically related to both. It is, however, contestable that genetic relatedness is a strong argument for allowing genetic modifications (Baylis 2013).

Following the supporters of GGE, editing the germline would also provide benefits on a population level (Powell 2015). Correcting a pathogenic genetic mutation in the germ cells of an individual patient means that the genetic errors disappear from the germline. Thus, the mutation is prevented from spreading within the gene pool of a given population. Disease prevention would benefit future generations, in addition to the individual affected by the application of GGE. This public health benefit has led to the call for a genome-wise program of GGE (Powell 2015). And this argument suggests that we are morally obliged to improve health outcomes for future generations. In addition, the implementation of a large-scale program would lead to an eventual decrease in healthcare costs. Taken in its totality, supporters of GGE claim that in the light of its public health benefits, this pursuit should be regarded as a moral imperative (Gyngell et al. 2017).

In order to decide whether the expected benefits of GGE outweigh the risks, we have to analyze the arguments brought forward by opponents and supporters of the method. The argument that implementing GGE means interfering with nature and therefore crossing a line that should not be crossed is not well-founded, since modern medicine implies interfering with nature on many levels already. As long as security standards are followed, there is no reason why interfering with nature for medical purposes should be prohibited in this specific context when it is accepted and well-established in others. Apart from medical risks, which clearly have to be diminished through further research, opponents of GGE also identify societal risks. The main societal risk is seen in the possible misuse of GGE for non-medically indicated purposes such as genetic enhancement. There is an ongoing debate whether genetic enhancement is ethically acceptable. This an issue that surely needs a focused analysis that cannot be given here. Apart from the question, whether we should accept genetic enhancement as such, there is the argument that neither our societies nor our legal frameworks are prepared for its impact (Lanphier et al. 2015). However, we are already taking precautions against the enhancing use of reproductive technologies. When it comes to PGD for example, there are legal restrictions in place in most countries that prohibit any non-medically indicated use. An analogous legal framework for GGE could be created. This can be considered as a practical argument following which the possibility of genetic enhancement is not a strong argument against GGE because it can be regulated when needed. Rules and regulations could be implemented in order to guarantee that GGE is only used in medically indicated cases. The differences between the cases do not only result from the nature of the procedure applied, but also from the moral status of the agent involved. Whether a medical intervention is to be considered as treatment or enhancement depends on the specific circumstances of the case. Each case where GGE is applied would have to be evaluated by an ethics committee, since there is no overall criterion to separate treatment from enhancement. This would have to be a case-to-case decision. Thus,

the argument following which the risk of misuse of GGE is too high has to be considered as non-convincing.

When considering the arguments in favor of GGE, we find that main benefit of GGE is seen in disease prevention for monogenic diseases (Gyngell et al. 2017; Powell 2015; Savulescu and Gyngell 2015). The argument implies that by using GGE, a future individual can be prevented from having a monogenic disease. This notion is valid with some restrictions. It is unproblematic as long as we deal with editing sperm cells or oocyte. In these cases, the pathogenic genes are eliminated or modified, so that they will not be transferred to the future individual. Thus, the future individual is prevented from inheriting the genetic defect. The matter is more complex, however, when we deal with zygotes. The edited zygote is only created because of the availability of GGE. The fact that GGE is available is the only reason a couple with pathogenic traits decides to create a zygote that is then immediately edited, thus producing an embryo without the pathogenic genetic trait. In other words, a zygote with a genetic defect is knowingly created in order to be edited at once. By stretching the boundaries of the term, this therapeutic procedure may also have the effect of disease prevention, particularly at the population level. The challenge here is the status of the zygote. If one considers the zygote as an individual, the term therapy may apply. If one considers the zygote as eukaryotic, diploid cell, it is unproblematic to call GGE disease prevention, since, analogous to sperm cell and oocyte-editing, a future individual is prevented from inheriting a monogenic disease. Given this definition, the term therapy would be misleading. The term therapy could only be used if an *in vivo* application of GGE was possible. Imagine the case where a life-threatening genetic defect is detected in an embryo in the womb by using prenatal genetic diagnosis. If GGE was applied here, given the technical feasibility which is unavailable at the moment, then we would deal with a life-saving therapy. Another possibility would be to classify GGE as an elaborate procedure of ART which is to fulfil one's wish to have a child. Both reproduction partners know about their genetic conditions. They know that if they reproduce, their offspring could inherit a pathogenic trait. Instead of using alternatives like gamete donation or adoption, they decide to create a zygote with the pathogenic trait that is altered afterwards. That means that there was no immediate need for intervening in the genome in the first place. These terminological issues may seem purely academic, but they may shape the development of clinical practice. Given a publicly funded healthcare system, it is to be expected that the question, whether or not GGE should be covered by the public health scheme, will arise. Usually, methods of disease prevention and therapeutic measures are covered by the public health scheme, whereas not all procedures of ART are financed by the public. In this regard, it may become important to clarify the status of GGE.

As noted, GGE could also be used as a means of disease prevention on a population level. However, it is doubtful how a large-scale use of GGE should be implemented without coercive measures. In order to be thoroughly effective, GGE may have to be mandatory for all carriers of certain genetic traits who want to

reproduce. That such a coercive, if not eugenic, measure would be implemented seems rather unlikely. Therefore, disease prevention on a population level may at most be considered as a side effect of GGE.

Do the benefits outweigh the risks?

It follows from our analysis that we can identify three types of risks: Firstly, there is a medical risk for the child that is created through GGE. Off-target effects and mosaicism are the crucial risk factors here. These risks are still prevalent despite recent refinement of GGE procedures. We are usually willing to take certain risks when a new method can be used to treat or prevent diseases that have so far been untreatable. As we have seen, the National Academies in the United States have suggested translational research on GGE which aims at a preventive use in cases of severe disease or disability where no alternative methods exist (The National Academies 2017). If we consider GGE as a possible means of disease prevention (notwithstanding the terminological difficulties outlined above), there are certain cases that fulfill these conditions, i.e. monogenic diseases like Huntington's. Since these conditions are usually severe and since there are no treatment alternatives, translational research efforts are justified. The same holds for infertility treatment. GGE is a promising method that allows couples with a known genetic risk to create healthy offspring that is genetically related to both partners. It can be used as an infertility treatment in cases where a genetic defect leads to infertile oocytes or sperm cells. As an assisted reproduction technology, GGE is certainly an alternative to available methods. It renders gamete donation obsolete and allows infertile partners to have a child that is genetically related to both of them. Regarding both disease prevention and infertility treatment, the main goal of the translational research will have to be the reduction of off-target effects and genetic mosaicism. However, it will be difficult to decide when an acceptable level of risk is reached. Whether the benefits outweigh the risks in this regard, however, depends on the outcome of future translational research.

Secondly, there is a medical risk for future generations. Since interventions in the germline mean that the modified genetic trait is passed on, errors in editing may have negative effects on future individuals. It is extremely difficult to predict which consequences genetic mosaicism for example will generate in one individual. It is even harder, if not impossible to foresee the effects in two or three generations. It is doubtful, whether further research will be useful here since effects on whole populations and in future generations are very difficult, if not impossible to model. However, if we consider that only a few individuals will use GGE, the risks at the level of the population must be put into perspective. The number of GGE-treatments might be small enough as to have no effect on the genome of a whole population (The National Academies 2017).

Thirdly, there are societal risks. GGE could be used for non-medically indicated purposes, first and foremost genetic enhancement. The majority considers genetic enhancement as a societal hazard

because it may compromise social justice and equality. However, this slippery-slope-argument suggests that the non-medically indicated use of GGE is a necessary consequence of its clinical implementation. This does not have to be the case since it is possible to create guidelines and regulations before GGE is implemented. This implies an intense ethical, legal, and public debate. Since the societal risks are manageable, they do not outweigh the benefits.

Conclusion

GGE offers promising possibilities for disease prevention and infertility treatment. The technique has been improved immensely in recent years and its medical risks have diminished. GGE might therefore be safe enough to be implemented in the clinic in the near future. Societal risk can easily be managed by implementing a regulative framework that limits GGE to medically-indicated uses. However, the effects of modified genes within the gene pool of a given population are unforeseeable and uncontrollable. It is almost impossible to predict which impact these modifications will have in future generations. When it comes to weighing risks and benefits, the question of scale is an important point. Given the treatment of one individual, we have sufficient data to assess the risks, e.g. for off-target mutations. This assessment becomes more difficult on a societal level, but is still possible, as long as a broad public debate takes place. But it is hard to see how such an assessment should be possible when the data simply cannot be retrieved sufficiently. Since the number of cases where GGE is applied will be small, there might not be an effect at all, but it is hard to say at the moment. Maybe future research will provide the means of calculating the effects of modified genes on a population level sufficiently. As long as this is not the case, the wish of few individuals to have a genetically related child does not outweigh the risks for a whole population.

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