The Ethics of Gene Editing

I. Introduction

In April 2015 it was announced that gene editing techniques had been used to modify the DNA sequences of human embryos for the first time.[1] The study by Liang and co-authors attempted to use the gene editing technique CRISPR to reverse the genetic mutations that lead to the disease muscular dystrophy. The study marked the first time the human germline – the DNA individuals pass to their children - had been intentionally modified.

The rise of gene editing technologies has been rapid. While crude genetic engineering technologies have been available for over two decades, early techniques did not have serious potential as clinically useful modifiers of human DNA. They relied on viruses to deliver novel genetic material to the cell. This often only changed one of the two copies of the target gene, meaning heterozygote animals had to be bred together to make modifications effective. Further this method was very imprecise, and made unintended changes to large segments of the genome. Consequently, only a small proportion of the animals that were the targets of these technologies did not suffer serious side effects.[2]

A revolution in genetic engineering started in 2010 with the development of techniques which used engineered enzymes, rather than viruses, to alter DNA. These techniques were given the collective moniker "gene editing" to reflect their increased efficiency and precision over older methods. In a very short space of time gene editing (GE) techniques have been used to make precise changes to the genes of yeast, plants, mice, rats, pigs, and primates.

While some have welcomed these technologies, others believe they raise serious ethical issues, particularly when used in human embryos. In this paper we examine some of the ethical objections that have been raised against germline gene editing. We distinguish between objections that centre on the use of human embryos for gene editing research, which we discuss in Part 2, and objections concerning the non-research applications of germline gene editing, which we discuss in Part 3. In Part 4 we outline an argument in favour of the gene editing. Finally, in Part 5, we compare gene editing with the dominant alternative means of avoiding genetic disease, genetic selection.

2. Objections to gene editing research involving human embryos

[1] Liang, Puping, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, et al. CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes. *Protein & Cell* 2015; 6(5): 363–72.

[2]

Gene editing research on non-human embryos has been relatively uncontroversial, but gene editing research on human embryos (a practice we label GERE) has been widely criticised.. These objections centre not on whether it would be ethical to use safe GE technologies, once developed, but whether it is ethical to conduct the GE research necessary to develop them. Some believe that as any GE research in humans would be unethical, whether the safe use of GE techniques to prevent disease is permissible is moot.

2.1 Safety

One argument against GERE is that this research cannot be conducted in a way that is safe for the embryo or the person that the embryo will become. The NIH points to "serious and unquantifiable safety issues", in justifying its negative stance toward gene editing research. Concerns for safety were also prominent in commentaries which appeared in *Nature* and *Science* calling for GERE to be halted or strongly discouraged.

The most obvious safety concerns regarding gene editing research stem from what is called "off-target" mutations – unintended changes to the genome. When used in other species, off-target mutations have been linked to cancer.[3]Gene editing performed on human embryos which will subsequently be brought to term therefore risks causing disease and disability.

Are the safety risks associated with off-target mutations strong enough to justify prohibiting, or strongly discouraging, GERE? This is a familiar question. Nearly all medical research poses safety risks to participants. Safety risks are therefore routinely considered as part of research ethics frameworks. Most standard research ethics frameworks assess safety risks by identifying who might be harmed and how.[4] When assessing the risks of GE research, we should be asking who will be harmed by cellular damage that could happen as a result of off-target mutations.

Some will say that the embryo itself is at risk of harm. But it is doubtful that the embryo is the type of entity that can be harmed. It does not have experiences or desires. As having good experiences and fulfilling desires are at least important elements of well-being, the embryo has either no, or a severally reduced, capacity itself to be harmed. Moreover, even if embryos can be harmed, it is doubtful whether harms to embryos have enough moral significance to justify prohibition or cessation of otherwise valuable research. Indeed, many jurisdictions currently permit embryo research that involves certain destruction of the embryo, and such is widely thought to be permissible. . . . Similarly, many jurisdictions allow destructive forms of contraception, such as intrauterine devices (IUD) and oral contraceptives, abortion, and the destruction of unwanted IVF embryos. It is doubtful that one could hold these practices to be permissible—as many do—while holding that the death of even an early embryo counts as a morally weighty harm.

[3] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3875854/#B21
[4] http://www.hse.gov.uk/risk/decide-who-might-be-harmed.htm

Finally, even if the death of an embryo does count as a morally weighty harm, this may not count against GERE in all circumstances. This is because, if human GE is developed to the point that it becomes safe for therapeutic uses, it could be used as a replacement for reproductive selection (discussed below), which itself often results in the discarding of excess embryos. Thus, development of human GE could potentially reduce the number of human embryo deaths that will occur in the future.[5]

It is harms to future people, not embryos, that are the most plausible basis for objections to GERE. If the embryos used in this research are brought to term, the children who are born as a result of these technologies could develop cancer or other diseases as a result of off-target mutations.

There is, however, an easy way to protect future people from the safety risks: ensure none are born. If no future children are affected by the research, then it has not been harmful to them. As long as GE results in off target mutations, we can ensure that these safety risks are mitigated by making sure that none of the embryos used in the research are allowed to develop to the point that they are the subjects of morally weighty harms.

The study by Huang and co-authors shows how the safety risks of GE can be negated. The study was not conducted on any embryos that were destined to be born, or indeed even had the potential to be born. The researchers used triploid embryos – embryos that have an extra set of chromosomes. These embryos are not viable, and normally spontaneously abort early in pregnancy. Moreover, these embryos were not created for the purpose of research, a practice some find objectionable, but were rather excess embryos created through IVF, and would otherwise have been destroyed. Trialing the CRISPR system in these embryos had no chance of resulting in a live birth. Although the study did find a high rate of off-target mutations, these did not result in morally weighty harms.

Regulations that govern embryo research in several countries that allow such research are already sufficient to protect future people from the safety risks of GE research. The UK, for instance, has laws allowing limited forms of genetic research to be conducted on IVF embryos, provided that the embryo is destroyed by 14 days and not implanted into a woman. [6] Given this legal requirement, and assuming complete compliance with the law, no GE research conducted in the UK risks harming any future child.

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[5] Savulescu, J. (2002). 'The Embryonic Stem Cell Lottery and the Cannibalization of Human Beings'. Bioethics. 16(6);508-29 (November). Whether this counts in favour of GEREwill depend on how we understand the supposed moral prohibition on killing human embryos. If we understand this as a deontological side-constraint, then it may not be possible to justify the killing of embryos now to avoid a greater number of embryo deaths in the future. By contrast, if the prohibition is an implication of a consequence-based duty to prevent harm, then the prevention of future embryo deaths could justify the causing of embryo deaths now.

[6] The Human Fertilisation and Embryology Authority, *Human Fertilisation and Embryology Act 2008*, Available at: http://www.legislation.gov.uk/ukpga/2008/22/pdfs/ukpga_20080022_en.pdf [Accessed 1 July 2015]

Some might worry that allowing human GE research under such a regulatory system will create pressure to relax laws in the future, and will thus lead to objectionably harmful research in the future. If the rate of off-target mutations significantly reduces, legislators may lift the 14 day limit and allow edited embryos to be brought to term. When this happens, one way it to minimize the safety risks associated with GE research will be to target imminently lethal conditions which would otherwise cause death soon after birth. The reason for this is if the GE technique turns out to be lethal, little is lost because that individual had no hope of survival. GE should initially be trialled in lethal catastrophic diseases.

In the history of gene therapy trials, this has not happened. The most infamous case is that of Jesse Gelsinger. In that case a somatic cell gene therapy was developed (not germline, as GE) for ornithine transcarbamylase deficiency, a disorder of nitrogen metabolism. The condition comes in two forms: mild, with normal life expectancy and management by diet, and severe, which is lethal in the first year.

Researchers, on ethical advice, decided to conduct the first trials in adults who were capable of consenting. Gelsinger consented at age 18 and died due to a catastrophic immune reaction. He had a normal life expectancy.

The trial should have been conducted in infants[7] as this would have minimized risk and resulted in less expected harm. The same principle applies to any trial of GE - the first trials ought to be conducted in diseases which a lethal soon after birth.

Indeed, other safety measures could be used to minimise safety risks for edited embryos resulting in live births. Testing of embryos and foetuses could be performed to evaluate the effectiveness of the GE. For example, PGD could be performed, with DNA analysis, at day 3-4, chorionic villus sampling (CVS) at 10 weeks and structural ultrasound at 20 weeks. If evidence of off target mutations were found, termination of pregnancy could be performed.

The safety risks associated with GE research therefore do not suggest that no GE research should be conducted at all, but rather suggest the research should be regulated in ways which mitigate these risks.

3. Objections to gene editing applications involving humans

3.1 No medical case

[7] Savulescu J. Harm, Ethics Committees and the Gene Therapy Death. *Journal of Medical Ethics*. 2001. 27: 148-150.

If proven acceptable safe, the most obvious application of GE will be to prevent genetic disease. Roughly 6% of all births have a serious birth defect, which is genetic or partly genetic in origin.[8] If we can identify the genes responsible for these conditions it will be possible to reverse these mutations through GE.

One of the objections to GE is that is unnecessary for this goal. Couples wishing to avoid genetic disease in their children can use in-vitro fertilization (IVF) to create multiple embryos, all of which can be tested for genetic disease before implantation. IVF and pre-implantation genetic diagnosis (PGD) are already widely used to avoid over 250 genetic diseases including cystic fibrosis, Huntington disease, haemophilia and phenylketonuria.

Marcy Darnovsky, the executive director of the non-for profit organization The Center for Genetics and Society, has claimed that "there is no persuasive medical reason to manipulate the human germline because inherited genetic diseases can be prevented using embryo screening techniques, among other means". This view was also expressed in a recent *Nature* commentary, whose authors stated that we "*cannot imagine a situation in which its use in human embryos would offer a therapeutic benefit over existing and developing methods."*

In fact, there is a strong medical case for using GE to prevent genetic disease. This is true of both of single gene disorders and polygenic diseases.

3.1A Single gene disorders

For some couples, using GE may be the only way they can avoid single gene disorders. Imagine a couple both of whom carry the gene for cystic fibrosis. They have a one in four chance of having a child with CF. They use IVF because they want to avoid having a child with this condition. However they only produce one viable embryo. Because this couple only produced one embryo, they will not be able to use PGD to avoid having a child with a cystic fibrosis. In these cases selection is not an option; however GE could be used to reverse any disease causing mutations. Even when couples can produce more than one embryo, in some cases selection will not avoid disease, for example when each partner carries predispositions to multiple conditions. In some jurisdictions, for example Germany, only one embyro can be produced and PGD is banned [check]

Another advantage GE has over selection as a treatment of single gene disorders is that it will reduce rates of genetic diseases in the next generation. PGD is not used to select against carriers of a condition, partly because this is often difficult to achieve with the number of embryos couples typically produce. Children who are born as the result of PGD are likely to be carriers of condition their parents selected against. GE will provide a way to remove disease causing genes from an embryo, and so the germ cells in that embryo will not carry the mutation . This will reduce the frequency of the disease in the next generation.

[8] The March of Dimes Birth Defects Foundation. *March of Dimes Global Report on Birth Defects*, New York: White Plains 2006. Harris (forthcoming)

These considerations show there is a strong medical case for using GE over selection to avoid single gene disorders in certain contexts.

3.1B Polygenic disorders

Most common diseases are not the result of single gene mutations. They are the result of polygenic disposition together with environmental influences. For example, genome wide association studies have identified at least 44 genes involved in diabetes;[9] 35 genes involved in coronary artery disease;[10] and over 300 genes involved in common cancers.[11]

It is less feasible (impossible using current techniques) to use selection techniques like IVF and PGD to target to polygenic conditions like this.[12] Say 20 genes contribute to a particular trait. If a couple want to use PGD to select for 20 different genes in an embryo, they would need to create around 10,000 embryos to make it sufficiently likely that one will have the right combination at all 20 loci. During routine IVF couples rarely produce more than 20 embryos (check). The chance of the couple having such a child would be just over 1% with traditional IVF and PGD.

Traditional selection methods are therefore not powerful enough to select against polygenic diseases. This is another reason why there is a strong medical case for preferring GE over selection. GE allows multiple changes to be made to a single embryo, and could therefore target many different genes simultaneously. GE could provide a vital tool in the fight against chronic diseases like cancer, diabetes and heart disease, diseases against which selection is toothless.

3.2 Germline changes and future generations

Another common objection that has been levelled against GE is that altering the germline will have negative consequences for future generations. This objection can take two forms: either GE will make unintended changes to the germline, through off-target mutations, which will have negative effects on future generations; or the changes we intend to make to the germline will have harmful unforeseen consequences.

In practical ethics, it is important to compare the proposed intervention to the status quo, not some idealized fiction. The status quo without GE is that future generations are already the victims of accumulating mutations. The germline is degrading as the pressures of natural selection are removed by treatment of

[9] Wheeler E, Barroso I. Genome-wide association studies and type 2 diabetes. *Briefings in Functional Genomics*. 2011;10(2).
[10] Peden JF, Farrall M. Thirty-five common variants for coronary artery disease: the fruits of much collaborative labour. *Human Molecular Genetics.* 2011; 20(R2).
[11] Chang CQ, Yesupriya A, Rowell JL, Pimentel CB, Clyne M, Gwinn M, et al. A systematic review of cancer GWAS and candidate gene meta-analyses reveals limited overlap but similar effect sizes. *European Journal of Human Genetics.* 2014; 22(3):402–8.
[12] Bourne, Douglas and Savulescu. Procreative beneficence and in vitro gametogenesis. *Monash Bioethics Review*. 2012; 30: 29–48.

infertility and disease [check and cite]. GE would correct this unnatural degradation of the human genome.

That said, it is not difficult to see how making many random mutations to the germline could be even more harmful to future generations. We may lose adaptive genes, while maladaptive genes become widespread. Random mutations may create new classes of late acting genetic diseases, which are not identified immediately and which accumulate in the genome.

The magnitude of the risk of random germline mutations is largely determined by the rate of off-target mutations, discussed in Section 2.1. If GE is likely to cause a high rate of off-target mutations, this will pose a risk not just to children who are born as a result of GE, but also to future generations.

However it is plausible that as GE develops the rate of off-target mutations will become negligible. The rates of off-targets mutation rate in animal models has been declining rapidly, and are now considered "rare" in some applications.[13] In addition, there will be ways to estimate the risk from off-target mutations. For example, whole genome sequencing, particularly of regions of the genome in which mutations are likely to be harmful could be performed using PGD after GE. Embryos with off target mutations would be discarded. This will further reduce the risks associated with off-target mutations on future generations.

Some may argue that even just a few germline changes could cause widespread harm to future generations. It is possible that these will be missed in any safety checks that are performed. However it seems unlikely that a small number of germline mutations pose a serious risk to future generations. Many other human activities result in a small number of germline mutations. For example, delaying paternity increases the number of mutations in sperm, which are then passed on to children in the next generation. Not many believe these mutations represent a significant risk to future generations. If they did, this would justify screening the sperm of older father for mutations, or providing incentives for young men to freeze sperm for use later in life.[14]

Furthermore, it is not normally thought that the risk of germline mutations is significant enough to block access to other treatments that cause them. Many treatments for cancer cause germline mutations. [15] However not many argue that these mutations cause a serious enough risk to future generations to screen the gametes of cancer survivors for mutations.

Therefore, if GE develops to the point where the number of off-target mutations is very small, the risk of harm to future generations is also likely to be very small. This risk is likely outweighed by the potential benefits of GE for future generations, discussed in Section 3.1

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[13] Iyer, Vivek, Bin Shen, Wensheng Zhang, Alex Hodgkins, Thomas Keane, Xingxu Huang, and William C Skarnes. "Off-Target Mutations Are Rare in Cas9-Modified Mice." *Nat Meth* 12, no. 6 (2015): 479–479.

[14] Although this has been suggested as a possible action. Ref JME sperm article

[15] http://www.nature.com/news/cancer-drugs-affect-mouse-genomes-for-generations-1.9930

A different concern about the effect of GE on future generation's centres on the intended, rather than the unintended, changes to we will make to the germline. Genes that are beneficial in one generation may be harmful in the next. Increasing the frequency of genes that are beneficial in one generation could have disastrous implications for the next.

Some genes provide protection against certain diseases but increase susceptibility to others. For example, it is known that a variant of the DARC gene – which codes for an antigen found on red blood cells – provides protection against malaria. However this version of the gene also disposes people to be more susceptible to human immunodeficiency virus (HIV). Suppose that in a region where Malaria is prevalent and HIV rare all parents use GE to give their children forms of the gene that respect against Malaria. Subsequent generations could then be decimated by HIV.

Other immune genes have known benefits but may also have costs that are yet to be discovered. For example, the CCR5 gene codes for a type of receptor found on macrophages (a type of white blood cell), which are targeted by the HIV virus. One form of the CCR5 gene provides resistance to the HIV virus. However, given the important role played by macrophage receptors in fighting other infections, it is possible that individuals with this form of the gene will be more susceptible to other infectious agents that are yet to evolve. If we use GE to introduce the HIV resistant version of the CCR5 gene, this may make future generations susceptible to a future plague.

There is no doubt that such concerns need to be carefully considered before GE is used in a clinical setting. Current decision-makers need to consider the interests of future generations, and should not reduce valuable forms of diversity. But these concerns don't show that GE is intrinsically harmful to future generations. Rather they demonstrate the need to take care in deciding when and how to deploy the technology.

3.3. Enhancement

One common concern about GE is that it will be used a tool of human enhancement and not merely to prevent disease. GE has much greater capacity to be used as a means of enhancement than conventional selection methods. This is because it can target a large number of genes simultaneously and could be used to insert genes that would not occur naturally.

Many believe that if GE were used a tool of human enhancement, it could cause widespread social harm. This seems to motivate Marcy Darnovsky, of The Center for Genetics and Society when she says that "creating genetically modified human beings could easily lead to new forms of inequality, discrimination and societal conflict."[16] It is difficult to see how using GE to avoid genetic *disease* could lead to any of these things.

[16] http://www.geneticsandsociety.org/article.php?id=8528

The ethics of human enhancement has been analysed in great detail elsewhere.[17] We believe that there are no reasons for thinking that biological enhancement is universally problematic, or invariably more problematic than non-biological enhancements, which are nearly universally rejoiced. However, even if biological enhancement were universally problematic, it is doubtful that this would count decisively against permitting GE research, given the potential therapeutic benefits. Many medical technologies currently being used or developed for the treatment of disease could also be used as enhancements, but this is not normally taken justify ceasing their development or use, even amongst opponents of enhancement. For example Lasik eye surgery, preimplantation genetic diagnosis, plastic surgery and sterilisation can be used non-therapeutically, but this fact is not considered to provide reasons to restrict their therapeutic uses. This is because regulatory tools can be used to limit enhancement uses to such a level that the moral costs of enhancing uses are outweighed by the benefits of therapeutic applications. There is little reason to suppose that the situation would be different for GE.

4. A moral imperative to develop and provide GE treatments

Imagine there is a genetic disease that causes a hole to develop in a baby's heart soon after birth. The condition is nearly fatal. A new treatment (T1) involves injecting enzymes directly in the heart after birth to prevent the hole from forming. This treatment cures 80% of cases, and has a low risk of side effects.

We can think of no reasons why T1 would be unethical, on the basis of the information provided. Indeed it is a moral imperative to provide T1.

Now imagine babies who will get this condition can be detected by an in-utero genetic test. Treatment T2 injects the exact same enzymes as T1, but does at the embryonic stage. This prevents the hole from forming in 80% of cases, it is has a low risk of side effects.

Are there any morally relevant differences between T1 and T2? Assuming T2 does not change the identity of the developing child[18], the only difference between the treatments is that T2 is applied in-utero and T1 one soon after birth. This seems morally irrelevant. Imagine we can only fund T1 or T2, and that T2 cures 85% of cases rather than 80% as in T1. In this case it seems we would have reasons to prefer T2 over T1.

Yet T2 is the equivalent of GE. GE is just an injection of enzymes at the in-utero stage. When done to prevent future disease, there is no clear morally relevant

[17] Savulesucu, Beucannon, Harris, Sandel, etc.

[18] It seems reasonable to assume that many in-utero changes do not affect the identity of the developing child. For example we normally think that a mother who drinks excessive amounts of alcohol in early pregnancy, harms a particular child, rather than altering the identity of the child she will have. We discuss the ethical significance of some of these considerations in Section 5.

difference between this and other treatments. One might argue that the fact T2 produces a heritable change, unlike T1, is morally relevant and counts against T2. As we argued in Section 3.2, we believe this reasoning is flawed. As T2 corrects the genes which cause this disease, individuals who have T2 will not be at risk of passing on the disease to their children. Individuals who get T1 remain at risk of having children with the same disease. This is an advantage of T2, not a cost.

Some may say it is not the T2's intended heritable changes that it less preferable to T1, but rather the unintended changes – the risk of random germline mutations. However, as we argued in Section 3.2, this is a risk that can be measured through genotyping and thus controlled.

In sum, it is plausible that GE-based treatments are morally equivalent to other medical treatments. Just as there is a moral imperative to develop new medical treatments for serious conditions, there is a moral imperative to develop GE based treatments for serious conditions.

One could respond by claiming the imperative to develop GE-based treatment is reduced because we already have genetic selection. As discuss in Section 3.1, GE will be able to treat a broader range of conditions than selection alone. However, there may other reasons to prefer GE-based treatment to selection based treatments – we look at this more closely in the next section.

5. Harms, benefits, GE and selection

Using GE to avoid disease is morally equivalent to standard treatments. However this not the case for selection.

Imagine a couple each of whom carries a cystic fibrosis (CF) gene. There is a one in four chance they will have a child with CF. Using IVF they are able to produce only a single embryo. They could use PGD at the 8 cell stage to test the CF status of the embryo, but they elect not to. They have the embryo implanted and carry it to term, and the woman gives birth to a child, whom they name Jim. It turns out the Jim is homozygous for the CF gene. He goes on to develop CF and lives only to the age of 20.

Has Jim been harmed by the parents refusal to employ PGD? Not in the normal, counterfactual comparative sense of harm. Assuming he has a life worth living, he has not been made worse off than he would otherwise have been, for he would otherwise have had no life at all; he would not have existed. Thus, had the couple employed PGD and discarded the affected embryo, they would not have averted a counterfactual comparative harm to Jim.

The standard way of understanding decisions of the sort made by Jim's parents is as causing impersonal harms, rather than person-affecting harm.[19] That is, they

[19] Though note that they could also be understood as involving *noncomparative* person-affecting harms . . .

do not make individual people worse off, but they do add to the amount of impersonal harm or badness in the world. Reasons to prevent impersonal harms have weight.[20,21] [cirte Parfit first, Reasons and Persons]Indeed, most decisions about distant future generations involve such impersonal reasons as the identity of the members of those generations is altered by the choices we make. Thus calls to reduce carbon emissions implicitly appeal to impersonal reasons, insofar as these actions may change who exists the future, and therefore may not benefit any particular individual.[22]

Consider now a variant of the case offered above. Imagine that a couple use IVF and produce a single embryo. A new test reveals that this embryo has CF. GE could be employed to correct the CF mutation and this would result in a healthy pregnancy and child. However, the parents elect not to pursue the GE procedure. They give birth to a baby, Jane, who goes on to develop CF and dies at the age of 20.

Has Jane been harmed, in the normal counterfactual comparative sense, by her parent's refusal to employ GE? She has. Had the parents employed by GE, by hypothesis, she have enjoyed a CF-free life rather than a live affected by CF. She would have benefitted from the GE in the same way that she would have benefited if she had been cured of her CF as a child, were this possible.

Thus there is a person-affecting reason to employ gene editing to prevent harm to Jane, but an impersonal reason to prevent Jim from coming into existence. How should these be weighted? Derek Parfit believes equally, and argues for this view with the following example.[23] Imagine two proposed medical programs have been proposed to reduce a particular handicap. The programs have identical costs.

If there is Pregnancy Testing, 1,000 children a year will be born normal rather than handicapped. If there is Preconception Testing, there will each year be born 1,000 normal children rather than a 1,000, different, handicapped children.

Parfit believes that these outcomes are morally-equivalent, and so there is no difference between person-affecting harms and impersonal harms.

[20] Savulescu J. Procreative Beneficence: Why We Should Select the Best Children. *Bioethics*. 2001; 15 (5): 413-426

[21] Savulescu J, and Kahane G. The Moral Obligation to Create Children with the Best Chance of the Best Life. *Bioethics* 2009; 23(5): 274-290

[22] Savulescu J. The Nature of the Moral Obligation to Select the Best Children. In *Future of Bioethics: International Dialogues*, Akira Akabayashi (ed), Oxford University Press. 2014. p.170 – 182.

[23] Parfit D. *Reasons and Persons.* Oxford: Oxford University Press; 1987.

This would also imply that there is as much reason to employ genetic selection as there is to employ a safe gene editing technique. If gene editing involves greater risks than selection, we should employ genetic selection.

However there are reasons to reject the view that person-affecting and impersonal benefits are always equivalent. Consider this case from McMahan:[24]

One can do either A or C but not both. The possible outcomes of one's choice are these:

A: P1 will later exist and live to 80	P2 will never exist	PE will live to 60
C: P1 will never exist	P2 will later exist and live to 60	PE will live to 80

If we only consider impersonal benefits A and C are equivalent. In each case our actions cause someone to live to 60, and another person to live to 80. On the No-difference view, the outcomes are morally equivalent.

But many will find this counter-intuitive. As McMahan explains "many believe it would be better to extend the life of an existing person than to ensure that a person who will have a longer life comes into existence rather than a person who would have a shorter life." In effect it seems wrong to make an already existing person die 20 years before they have to, just to make sure a longer-lived person to comes into existence rather than a different, shorter-lived person. In this way, we might think that person-affecting reasons are stronger than impersonal reasons – at least in some cases.[25]

This would give us a reason to prefer gene editing rather than selection because the former prevents a person-affecting harm while the latter does not.

However, just as the harms prevented by GE may be more important than those prevented by genetic selection, so too may any harm *caused* by GE may be more serious than equivalent harms caused by selection.

Imagine a deaf couple wishes to have a deaf child. There are two ways in which they could do this. The first is by genetic selection. They could have IVF and test the embryos. They could deliberately select a deaf embryo and have a deaf child, Danny.

Or they could use GE to insert genes that cause deafness into an embryo which would have developed into a child who had normal hearing. Call this child Doris.

Consider the perspective of the child. First, Doris. Has Doris been harmed and does she have a ground for complaint? Yes - she can complain that were it not for the actions of her parents, she (Doris) could have had a better life as a hearing individual. She has been harmed. In this way, using GE to change Doris genes so

[24] McMahan 2013, c

[25] See also Temkin, L. *Rethinking the Good: Moral Ideals and the Nature of Practical Reasoning*. Oxford: Oxford University Press; 2012. Pp….

that she will become deaf is the same painlessly cutting the auditory nerves of a child to cause deafness.

What about Danny? If his parents had not selected him as a Deaf child, he would not exist. He has not been harmed by selection and cannot complain if his life is worth living.

This decision to use GE to create a deaf child therefore seems more criticisable that the decision to use selection to create deaf child.

Moreover, genetic selection minimises person-affecting harm in cases of uncertainty in the following way.[26] Imagine we identify some gene for manic depression. However, this gene also disposes to creativity. Not knowing of the beneficial effects, we try to eradicate this gene.

In the case of gene editing, an embryo has the gene for manic depression corrected. This results in an individual without mental illness but who is uncreative. Vincent.

In the case of selection, we select a normal embryo that turns out to be uncreative. Vicky.

Now can Vincent complain he has been harmed? In some cases, yes - if the balance of benefits of creativity outweigh those of mental illness. What about Vicky? No - she can only complain if her life is so bad it is not worth living. This is likely to be an extremely rare event.

It is unclear how to weigh these different considerations. Failing to engage in GE results in person-affecting harm in a way that selection does not, but engaging in GE also risks person-affecting harm in a way that selection does not. How we should balance these considerations may depend on whether we should regard causing harm to be more morally grave than failing to prevent it. If we should, and if one is uncertain about the unintended consequences of targeting genes through selection or editing, it may be that one should opt for selection.[27] However, if the risk of unintended consequences is very low, it becomes more plausible that one should opt for GE over selection, even if causing harm is morally worse than failing to prevent it.

5.2 Policy considerations

If we move to the level of policy, matters become even more complicated.

[26] Savulescu J, Hemsley M, Newson A, Foddy B. Behavioural Genetics: Why Eugenic Selection is Preferable to Enhancement. *Journal of Applied Philosophy*. 2006 23 (2): 157-171.
[27] Savulescu J, Hemsley M, Newson A, Foddy B. Behavioural Genetics: Why Eugenic Selection is Preferable to Enhancement. *Journal of Applied Philosophy*. 2006 23 (2): 157-171.

Adopting a policy of allowing gene editing may be identity determining for the children who are born as the result of GE. Let's compare the world with and without such a policy.

Imagine there is no gene editing. A couple have a child Sarah, either using natural methods or genetic selection.

Now suppose a policy is introduced to allow gene editing, and that because of this, the gametes used in an IVF cycle are screened slightly differently.[28] This creates a different embryo, Harry. Harry would not have existed were it not for the policy of gene editing; Sarah would have. Thus any harms and benefits that fall on Harry will not be person-affecting.

Say as a side effect of GE, Harry develops cancer of the arm. Has Harry been harmed by the policy which allowed GE? Were it not for such a policy, he would not have been born. Thus, provided the cancer of her arm does not render his life not worth living, the policy of allowing GE has not caused Harry to be harmed, in a person-affecting sense.

Similar thoughts apply to the prevention of harm. Say Harry would have developed cystic fibrosis if GE had not been performed. Has the policy that allows GE prevented him from being harmed? Again it seems not in a person-affecting sense. If were not for the policy, Harry would not have has CF. He simply would not have existed.

This is the non-identity problem at the level of policy.

What are the implications of a policy of gene editing being identity altering?

One of us has elsewhere argued that we have significant moral reasons to select the best child—the principle of Procreative Beneficence.[29,30] PB generates impersonal reasons. If these reasons are weaker than person-affecting reasons, this has significant policy implications. For example, it may imply that, although failing to have the best child is inconsistent with one significant moral reason, people should be permitted to act against this reason if they wish. Thus, deaf people should be allowed to select a deaf embryo, even though there is an

[28] It should be noted that it is unlikely that a policy of GE would change the identities of all of the future people who are affected by the policy. It is unclear whether gene editing would require different gamete screening to standard IVF practices, or how a policy of allowing gene editing would change the timing of when couples undergo an IVF cycle. However it is very likely to change the identity of some future people. It thereby represents an "imperfect" non-identity problem (ref Cohen).

[29] Savulescu J. Procreative Beneficence: Why We Should Select the Best Children. *Bioethics*. 2001; 15(5): 413-426.

[30] Savulescu J, and Kahane G.The Moral Obligation to Create Children with the Best Chance of the Best Life. *Bioethics*. 2009; 23(5): 274-290

impersonal moral reason to have a hearing embryo.[31] For gene editing policies which are identity altering, it implies that we could tolerate more, rather than less, risk associated with gene editing research and application. Despite calls for higher safety standards to be applied to gene editing research,[32] the fact that a policy of allowing gene editing can be identity altering might permit more risky research to be preformed compared to other research or novel therapy that involves person-affecting risk of harm.

Conclusion

In this paper we have shown that GE research can be conducted safely in ways that carry few risks. This of course would be moot if the development of GE carried no benefits. But we have shown here is a strong medical case for GE to combat single gene disorders and polygenic disorders. In addition, as GE based treatments are morally equivalent to standard treatments we have a moral imperative to develop and pursue them.

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[31] Savulescu J. 'Deaf lesbians, "designer disability," and the Future of Medicine'. *British Medical Journal*. 2009; 325(7367):771-3.
[32] Baltimore D, Berg P, Botchan M, Carroll D, Charo A, Church G, et al. Biotechnology. A Prudent Path Forward for Genomic Engineering and Germline Gene Modification. Science. 2015; 348 (6230): 36–38.