Moral Imperative to Gene Edit

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Selection vs Gene Editing?

- “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”
  - Marcy Darnovsky, the executive director The Center for Genetics and Society
- 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.*"

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Target Article

Reasons and Reproduction: Gene Editing and Genetic Selection

Jeff McMahan & Julian Savulescu

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Abstract

Many writers in bioethics, science, and medicine contend that embryo selection is a morally better way of avoiding genetic disorders then gene editing, as the latter has risks that the former does not. We argue that one reason to use gene editing is that in many cases it would be *better* for the person who would develop from the edited embryo, so that not to have done it would have been *worse for* that person. By contrast,

3 Positions on Reproductive Reasons

1. Person-Affecting
2. Impersonal
3. Person-Affecting Priority

Education And Debate

Deaf lesbians, "designer disability," and the future of medicine

BMJ 2002 ; 325 doi: https://doi.org/10.1136/bmj.325.7367.771 (Published 05 October 2002)
Cite this as: *BMJ* 2002;325:771

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The topic of this article is the subject of a debate in this month's issue of Journal of Medical Ethics. Go to jme.bmjjournals.com to read the debate in full

With the completion of the human genome project, the genetic basis of disease is becoming better understood. Genetic tests for disabilities are increasingly becoming available to allow couples with a family history of genetic disease to select healthy offspring. But some couples wish to select for disability. Might there be good reasons for acceding to such requests?

A deaf lesbian couple in the United States have deliberately created a deaf child. Sharon Duchesneau and Candy McCullough used their own sperm donor, a deaf friend with five generations of deafness in his family. Like others in the deaf community, Duchesneau and McCullough don't see deafness as a disability. They see being deaf as defining their cultural identity and see signing as a sophisticated, unique form of communication.[1–3] (See box 1

Choosing Deafness

- Deafening a hearing embryo or child
  - Person-Affecting Harm
- Selecting for a deaf embryo:
  - Impersonal harm
  - No person affecting harm

- Person-Affecting reasons stronger than impersonal reasons
- So it should be illegal to deafen a child but legally permissible to select a deaf embryo because it involves “harmless wrongdoing.”
  - UK law is wrong

- Savulescu J. Deaf lesbians, “designer disability,” and the future of medicine *BMJ* 2002; 325 :771 doi:10.1136/bmj.325.7367.771

The Power of Impersonal Reasons: Zika

- Mosquito borne virus that causes microcephaly and intellectual disability in fetuses affected in gestation
- Public Health England and CDC: “Wait 3 months before attempting to conceive after visiting a region affected by Zika.”
- Non-identity problem: failing to wait does not harm anyone because it changes who comes into existence – impersonal harm
- Impersonal harm justifies obligations to future generations(climate change)

Procreative Beneficence (PB)

- couples (or single reproducers) should (have good normative reason to) select the child, of the possible children they could have, who is expected to have the best life, or at least as good a life as the others, based on the relevant, available information.

Julian Savulescu

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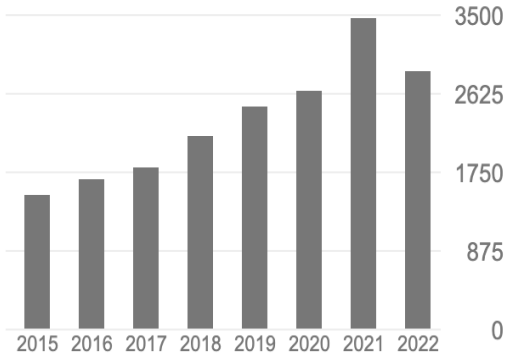

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Implications of Impersonal Harm/PB

- Should/moral obligation to select against:
  - Severe diseases
  - Mild diseases
  - Late onset diseases
  - Treatable diseases
  - Higher risk of disease
  - Non-disease traits like low normal intelligence that lower the chances of well-being

Implications for Gene Editing vs Genetic Selection

- Gene Editing provides person-affecting benefits
- Genetic selection does not benefit any person – it changes who comes into existence
- Gene editing is superior in an important philosophical way

	PA	I	PAP
Wait (Zika)	0	++	+
Select H vs D	0	++	+
Select D vs H	0	——	—
Cure (GE)	++	++	++
Deafen	——	——	——
Non-Directive Counselling	++	——	—
S vs GE	GE	GE=S	GE>S

Table. Reproductive Reasons

Moral imperative to gene edit

- Imagine there is a pill which will cure cystic fibrosis
- It would be wrong of parents to refuse such a pill for their child
- Doctors should seek a court order to administer the pill
- Gene editing is the ultimate cure for genetic disorders – it corrects the abnormality in every cell
- Doctors should seek court orders to do gene editing in those who refuse selection once it is safe
- Gene editing is different to genetic selection: a future child can justifiably complain, “You should have tried to cure my genetic disorder.”

Selection vs Gene Editing?

- “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”
  - Marcy Darnovsky, the executive director The Center for Genetics and Society
- 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.*"

WRONG!

- 3 groups who should consider gene editing now:
  1. Those with limited numbers of embryos all affected by severe genetic disorders
  2. Couples homozygous for a genetic disorder
  3. **Those with religious or moral objections to genetic selection or embryo/fetal destruction** – ultimate treatment

- The worse the genetic disorder, the stronger the reason to attempt gene editing

The Major Reason to Gene Edit: Polygenic Conditions

- genome wide association studies
  - 44 genes involved in diabetes;
  - 35 genes involved in coronary artery disease;
  - 300 genes involved in common cancers.

- It is impossible using current techniques to use selection techniques like IVF and preimplantation genetic testing to target to polygenic conditions like this.
  - 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.

Potentially Massive Changes from Polygenic Editing

- Alzheimer Disease: gene editing at only 23 loci (including APOE 4) is predicted to decrease lifetime prevalence from 5% to 0.3%. A large proportion of that reduction is due to the APOE variant
- For Type 2 Diabetes, Coronary Artery Disease and Schizophrenia, editing all known GWS loci (genes) is predicted to lead to a negligible prevalence of disease among edited genomes.
  - Visscher et al*, Nature,* forthcoming
- Likewise, the predicted changes for the quantitative traits are extremely large.
  - For example, the results predict an increase in IQ of 5 standard deviations, or 75 IQ points, if all known GWS loci (genes) are edited, and the results for height are even more extreme.

Virtually Impossible to Achieve Naturally

- Note that there may be individuals in the current population who are homozygous for the protective allele for all of these 10 loci.
  - For example, that probability is 1 per 2 billion for Alzheimer Disease
  - 1 per 3 billion of Schizophrenia
  - 1 per million for Manic Depression

Objection: Gene Editing is Identity Altering

- Child would not exist if were not for gene editing

  Sparrow, Douglas and Devolder

  Alonso M, Savulescu J. He Jiankui´ s gene-editing experiment and the non-identity problem. Bioethics. 2021 Jul;35(6):563-73.

Response to Douglas-Devolder

- Gene editing is just like a medical treatment.
- Imagine a drug is developed that replaces the missing protein (which gene editing would also produce). However, there are some risks.
- A couple who carry CF gene were considering not having a child because they didn't want to run the risks of the child having CF and weren't prepared to use PGD or PND.
- But now the drug is developed they consider having a child. They intend to have one because they believe the drug would be beneficial for the future child. But at the last moment the risks loom larger, and they change their mind.

- On their analysis, the drug does not provide person affecting benefits. But it clearly does. The fact that people might choose not to conceive if they consider the risks too great doesn't affect it as a medical treatment. Gene editing is the same as the drug.

Douglas' Response

- If the drug is administered after the point that the person comes into existence, this case is different from gene editing. At that point, the alternative to administering the drug still involves the person existing and either having CF or a very short life. On the other hand, we assume that the gene editing occurs in the early embryo and that the early embryo is not yet the person. Thus, discarding the embryo at that point results in non-existence of the person, and in many cases non-existence is indeed what would happen if the gene editing doesn't occur (e.g. because the parents decide at the last minute that it's too risky).
- But yes, if the drug only had to be administered once in the early embryo, the case would be the same as our gene editing example. In that case, if the parents would discard the embryo if they didn't give the drug, then we indeed claim there is no person-affecting benefit. Maybe that's a bit counter-intuitive, but intuitions are often misleading in different-number cases. I think intuitions are misleading in this case because our intuitions are driven by thinking of existence with CF as the relevant alternative. But on our view one shouldn't think of that as the relevant alternative if the parents would neither (a) in fact nor (b) be morally required to bring the embryo into existence if they don't edit it.

Conclusion

- Gene editing should be attempted in a staged way
- Minimize expected harm
  - Start with catastrophic radically life-shortening diseases
  - When it is shown to be safe in these, progress to severe single gene childhood onset diseases
  - Then to adult onset single gene disorders
  - Then to dispositions or polygenic conditions
  - Finally enhancement of well-being promoting traits

- Gene editing benefits future people; genetic selection replaces them

Gene Editing

“China Condemns Baby Gene Editing Scientist” BBC
“Gene-editing Chinese Scientist He Jiankui Could Face Death Penalty” ABC
“China’s gene-edited babies may have been given boosted intelligence” News.com.au
“‘Gene-edited babies’ is one of the most censored topics on Chinese social media” Nature
“Scientists call for global moratorium on gene editing of embryos” The Guardian

Note: enhancement, not treatment

Monstrous Gene Editing Experiment Press Release

• Chinese researcher He Jiankui of Shenzhen claims to have gene edited two healthy embryos, resulting in the birth of baby girls born this month, Lulu and Nana. He edited a gene to make the babies resistant to HIV. One girl has both copies of the gene modified while the other has only one (making her still susceptible to HIV).

•If true, this experiment is monstrous. The embryos were healthy. No known diseases. Gene editing itself is experimental and is still associated with off-target mutations, capable of causing genetic problems early and later in life, including the development of cancer. There are many effective ways to prevent HIV in healthy individuals: for example, protected sex. And there are effective treatments if one does contract it.

- This experiment exposes healthy normal children to risks of gene editing for no real necessary benefit.
- It contravenes decades on ethical consensus and guidelines on the protection of human participants in research.
- In many other places in the world, this would be illegal, punishable by imprisonment.
- These healthy babies are being used as genetic guinea pigs. This is genetic Russian Roulette.

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EDITORIAL 1

Future directions of the journal (1 June, 2001) FREE

Julian Savulescu

EDITORIAL 2

Harm, ethics committees and the gene therapy death (1 June, 2001) FREE

Julian Savulescu

Jesse Gelsinger

- an 18 year old man with mild ornithine transcarbamylase (OTC) deficiency, a disorder of nitrogen metabolism.
- controlled by diet and drug treatment.
- Sept 13, 1999, James Wilson's team at the University of Pennsylvania's Institute for Human Gene Therapy (IHGT) injected 3.8 X 10^{13} adenovirus vector particles (one of the highest doses)

Gelsinger

- virus particles were injected directly into the major artery to the liver.
- died 4 days later
- first death directly attributed to gene therapy.

Infants or Adults?

- Newborns with a severe form of the OTC deficiency are likely to die early in life
- Adults with mild OTC deficiency like Gelsinger can leave a reasonable quality of life on diet and drug therapy.
- Should the trial have been performed on severely affected newborns or mildly affected adults?

The Justification for Adult Participation

- “There are serious risks including a risk of death associated with participation in this trial. Since the risks are significant, it is better that the trial be conducted on humans who consent to those risks rather than on those who cannot consent.”

- Consent prioritised over harm

Mildly affect adults or severely affected newborns?

- *Put simply, Gelsinger had something to lose while the seriously affected newborn did not.*

- There is no good reason to prefer more harm to less harm, regardless of whether someone is prepared to consent.

Nature, Nov 28, 2018: "Translational Pathway"

- "In the opening presentation of the day, George Daley, dean of Harvard Medical School in Boston, Massachusetts, pointed to **Huntington's disease or Tay–Sachs disease as examples of diseases** that, in some circumstances, might be averted only through gene editing."

- "Fears are now growing in the gene-editing community that He's actions could stall the responsible development of gene editing babies. In a lecture on the second day of the summit, ahead of He's talk, Daley urged support for pursuing germline gene-editing research despite recent events."

    - "It's possible that the first instance came forward as a misstep, but that should not lead us to stick our heads in sand and not consider a more responsible pathway to clinical translation," he said.

5 Stage Translational Pathway and Expected Harm

1. Terminal conditions in early life
    - Tay Sach's Disease
    - BRAT-1
        - This could be attempted now

2. Conditions which undermine development of autonomy and rational agency [shortening of life and severe cognitive impairment]

    - Fragile X syndrome
    - Down Syndrome

5 Stage Translational Pathway and Expected Harm

3. Non-avoidable serious risk
    - Cystic Fibrosis,
    - Huntington Disease

4. Avoidable (by acceptable non-genetic interventions - eg social) serious risk
    - immunity to infection (resistance to HIV)
    - decreased probability of chronic disease (polygenic interventions),

5. Enhancement of normal characteristics - unavoidable risk to well-being or autonomy
    - Enhancement of “low normal IQ” (IQ 70-85)

Testing for Safety

- Can assess off target mutations or mosaicism through:
  - Preimplantation genetic testing of blastocyst
  - Prenatal Testing of fetus
  - etc

Philosophical Reason to Gene Edit

- Provides “person-affecting” benefit rather than impersonal benefit

"*The 14-Year-Old Girl*". This girl chooses to have a child. Because she is so young, she gives her child a bad start in life. Though this will have bad effects throughout this child's life, his life will, predictably, be worth living. If this girl had waited several years, she would have had a different child, to whom she could have given a better start in life."

Derek Parfit, *Reasons and Persons*

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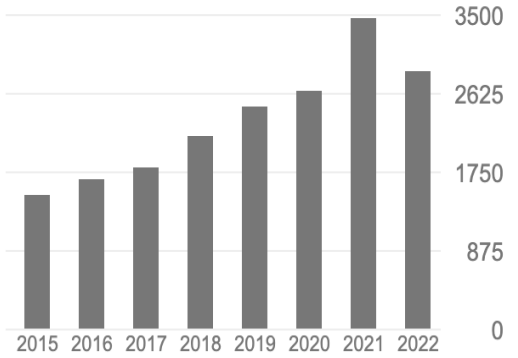

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