The Clinical Utility Problem for Germline Genome Interventions

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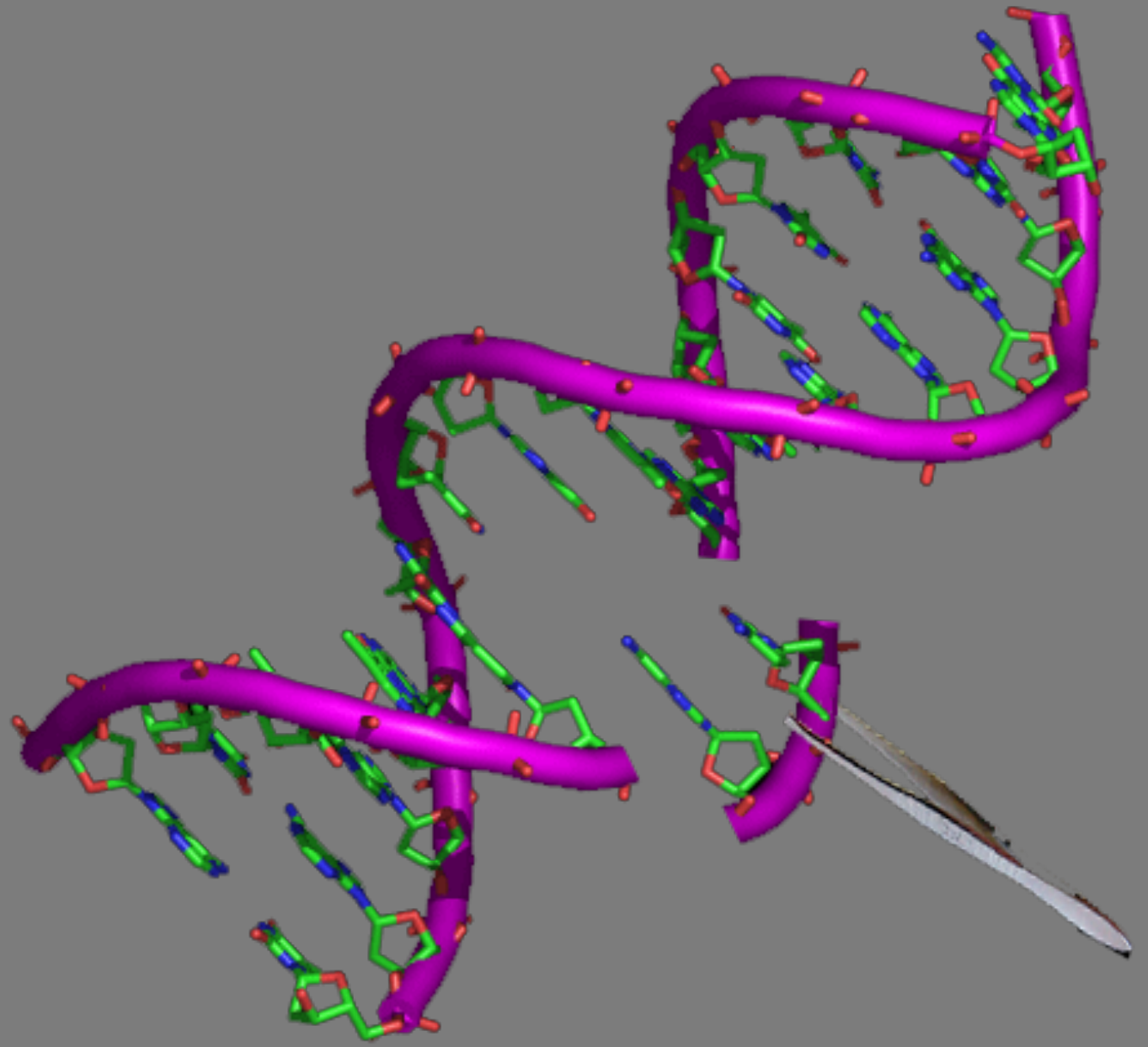

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A Sea Change?

"It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved…and (ii) there is broad societal consensus about the appropriateness of the proposed application."

First International Summit, 2015

"…the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials."

Second International Summit, 2018

And even further in NAS 2020, new draft ISSCR guidelines; not everyone happy about this (e.g. Baylis 2021)

"Genetic engineering, when fully developed...will be able to make changes that can be transmitted to succeeding generations and create new capacities, and hence to establish new norms of health and fitness."

Leon Kass, "The New Biology", *Science*, 1971

"On the ethics front...Of greatest concern is editing of genes to confer advantageous traits not related to avoiding disease or preserving health. Efforts to optimize traits such as intelligence, memory, creativity, bravery or strength raise the specter of eugenics..."

Daley et al, "After the Storm", *NEJM*, 2019

"With time and experience, the express goal of human genome editing would become one of human transformation. The modern eugenic project could be imposed top-down by an autocratic government intent on improving it's populations genetics…Or in addition, eugenic goals might be advanced unwittingly by prospective parents exercising their so-called reproductive freedom."

Baylis, *Altered Inheritance* (Harvard, 2019)

Order of Business

1. Clinical Utility and 4-D Framework
2. 3 Questions About Clinical Utility for GGE…
3. …and 2 Overarching Philosophical Issues about Emerging Biomedical Technologies
4. Sketch of A Possible Position

Exercise does not involve *endorsement* of use of HHGE one day; only way to figure out if it *should* be done is to envision *how it could be done responsibly* and decide if that is justifiable (or even desirable) (Cwik 2021)

Clinical Utility

International Commission Report (NAS 2020) Recommendation 4:

"Initial uses of heritable human genome editing (HHGE)…should be limited to circumstances that meet all the following criteria:

- The use of HHGE is limited to serious monogenic diseases…[defined as] one that causes severe morbidity or premature death
- The use of HHGE is limited to changing a pathogenic genetic variant…to a sequence that is common in the relevant population…
- No embryos without the disease-causing genotype will be subject to the process of genome editing and transfer…and
- …the use of HHGE is limited to situations in which prospective parents: (i) have no option for having a genetically-related child that does not have the serious monogenic disease…or (ii) have extremely poor options

Clinical Utility

Such statements raise more questions than they answer:

- What is a "serious monogenic disorder" (as opposed, say, to an insufficiently serious one)? – Cystic fibrosis? Achondroplasia? Nonsyndromic hearing loss?
- What are the index sequences for determining "common genetic variants"? How do you tell when a "pathological genetic variant" has been changed into a "common" one (and not, say, a problematically uncommon but non-pathogenic one)?
- Why is having a "genetically-related child" a sufficient clinical goal? What makes other options "extremely poor" compared to HHGE?

Clinical Utility

Clinical Utility Problem:

HHGE is guilty until proven innocent (because of "specter of eugenics" etc.) – use is justifiable if

- There is sufficient clinical benefit; and
- The benefit justifies use of HHGE vs. other available options; and
- Use of HHGE can be restricted in practice to permissible uses (like treatment of "serious monogenic disorders") and not used to, e.g., "optimize traits"

4-D Framework (from Cwik 2020)

Target	Specific gene(s) whose function the intervention aims to alter	*MYBPC3*[1], *HBB*[2]
Goal	Intended change in function and intended phenotypic effects	Replace *MYBPC3* with non-pathogenic allele[1], induce deletion in *CCR5*[3]
Outcome	Full suite of effects resulting from intervention, intended or otherwise	Impacts of *CCR5* on neurological development[3], potential pathogenicity of off-target effects[1-2]
Mechanics	Specifics of techniques used to alter function of targeted genes	CRISPR[1-3], oocyte spindle transfer[4]

[1]Ma et al 2017; [2]Liang et al 2105; [3]Cyranoski and Ledford 2018; [4]Zhang et al 2017

3 Questions About Clinical Utility

1. What goals and outcomes can HHGE be used for?
   - Which conditions are "serious"? Which are best addressed through GGE? Which are best addressed through neonatal gene therapies? PGD?
   - Important connection to justification of translational research

2. What genes can be targets?
   - Ex. The "*CCR5* Problem"

3. Why do it at all?

2 Objections

3. Why do it at all?

Obj. 1: "Cui Bono?"

"[HHGE] is not a cure or a treatment. It is a selective reproductive technology. It is deployed as part of a process that creates children whose existence is not inevitable from modified gametes and embryos. Their coming into existence is dependent on the choice to use [HHGE] in creating them in the first place. Thus, [HHGE] is a means for creating healthy lives…But it is highly controversial to endorse the view *that we have any moral reason* to create healthy lives for their own sake." (Rulli 2019, my emphasis)

2 Objections

3. Why do it at all?

Obj. 2: What Value in Genetic Parenthood? (Botkin 2020, Baylis 2019)

- HHGE is for having disease-free genetically-related child
- Other ways to parent a genetically-related child (PGD, gamete donation) or just parent a child (adoption, co-parenting)
- Parenting a genetically-related child is a *preference*, not a sufficient reason to justify HHGE (e.g. Baylis 2021: "…the desire for healthy, genetically-related children is just that – a desire, not a need.")

Sketch of a Possible Position

- Why should translation and possible clinical use of HHGE have to satisfy desiderata other emerging biomedical technologies do not?
- Given tenor of current research, burden of proof really seems to be to show that HHGE raises "specter of eugenics" etc. and is guilty until proven innocent, rather than other way around
- Reproductive issues and presence of heritable genetic disorders are recognizable medical needs; prevention of disease is a recognizable medical goal
- Philosophical objections to these involve imposing judgments about *who should get treatment* on existing patients
- In other areas, this is unacceptable (ex. judgments about beef eating and cardiac disease)

Some Bigger Philosophical Issues

- Novel biomedical technologies are resource-intensive to develop, involve (potentially) difficult clinical research to test, and are likely to be expensive and have limited access – what situations justify developing such tech?

- For any novel biomedical technology to even be in the game, must be (some, sufficient) clinical utility; but what medical problems are sufficiently pressing to justify such investment? For that matter, what things that we currently consider medical problems *really are* problems, when we consider what it would take to devise novel interventions for them?

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Thanks!

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