Case: The selfish gene editor

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Innovations in gene editing technology

Gene sequencing and manipulation have a long history in genetic engineering, but a technology co-invented by the Doudna lab at UC Berkeley is revolutionizing the field. The breakthrough technology is CRISPR-Cas9, which allows for cutting DNA molecules in very specific locations.[1] This "is the most versatile genomic engineering tool created in the history of molecular biology to date."[2] Given this new technology, for some, gene editing "will change everything forever."

The CRISPR-Cas9 technology has unimaginable potential, ranging from improving crops to resurrecting extinct species to fighting disease.[3][4] A powerful research tool,[5] the technology is attracting attention from biotech companies and venture capitalists. Because gene editing can eliminate mutations responsible for disease, it could help a grown person avoid disease, and when applied to the genetic material of an embryo, preemptively protect the person who will be born. It is possible not only to eliminate a disease, but also to "enhance" the organism, by changing physical attributes in desirable ways.

Gene editors can target somatic cells and modify features in a living organism. Because somatic cells are not involved in reproduction, the genetic changes are not passed on to offspring. But it is also possible to target germ-line cells — also known as gametes — which are involved in reproduction. When germ-line cells are altered, the changes are passed on to offspring, and become part of the genome of future generations.

The ethical implications of gene editing are the subject of a heated debate. How far to push innovation, and how fast to go? The stakes are high, and the incentives to be "first" are strong. For scientists, discovery yields glory, grants, and sometimes patents. Patents are also important to universities and firms. Firms value a prime-mover advantage — developing capabilities before others establish preeminence in an industry and ultimately market leadership and profits. Assisted reproduction is a growing industry, and the potential looms large to augment the

[1] CRISPR stands for Clustered Regularly Interspersed Short Palindromic Repeats, and reflects the fact that DNA in certain bacteria contain symmetric sequences of DNA bases evolved as a defense against invading viral DNA. The breakthrough took place through the realization that the Cas9 (for CRISPR-associated 9) enzymes could be used to guide CRISPR sequences to cut DNA and allow for deletion or insertion of DNA material.
[2] Brokowski and Adli 2018, "CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool," *Journal of Molecular Biology*.
[3] Tangermann 2018, "A CRISPR Future: Five Ways Gene Editing Will Transform Our World," in futurism.com.
[4] Hsu et al 2014, Development and Applications of CRISPR-Cas9 for Genome Engineering. *Cell* 157(6).
[5] Greenfield 2018, "Carry on editing," *British Medical Bulletin* 127(1).

business with "designer human" services.[6] One can imagine a world in which clients routinely shield their offspring from disease, and also choose their skin color, height, athleticism or IQ.

While the benefits of a particular genetic alteration may be clear, the risks are not. One concern is that it is easier to use the technology than to understand its full consequences.[7] Scientists worry that gene edits may have unintended side effects. The gene editor may inadvertently make "stray edits." And the intended edits themselves may have unforeseen effects. When it comes to germ-line editing, the unintended effects may only become apparent generations after initial gene editing took place.[8]

A doctor and a patient considering somatic gene editing can have a conversation about how best to balance the potential risks and benefits. That conversation is not possible when embryos and future generations are involved through CRISPR Germline Editing Therapies (CGET). According to Evitt et al (2015),

> Normally, an institutional review board (IRB) would be responsible for regulating early-stage human therapeutics research. Since embryos are not considered human subjects and are not afforded the same protections outlined by the Belmont Report (e.g., autonomy, informed consent), CGET research does not fall clearly under the purview of an IRB. Furthermore, IRBs are prohibited from considering long-term social ramifications when deciding to approve research.

Yet it is unclear how much science should be paralyzed by some of these concerns. Consent from embryos maybe an irrelevant consideration because it simply cannot be obtained. After all, parents make decisions on behalf of their children, current and future, all the time.[9] The view is possible that not only is germ-line editing not to be forbidden, but that we may have a duty to future generations to produce the best possible babies we can.

Some scientists — including CRISPR/Cas9 co-inventor Jennifer Doudna — advocate for treading slowly.[10] Some argue that research should first proceed by more completely understanding the effect of germline modification in animal models (for instance, by performing more experiments with mice or monkeys). Human trials involving pregnancy can be contemplated only after progress made with simpler models tells us that risks are low enough. Others endorse research with human embryos that will not result in pregnancy, or when there is an extremely compelling medical reason.[11] According to van Dijke et al (2018), a survey of the emerging debate in scientific journals raises various dimensions of concern:

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[6] Laura Hercher, "Designer babies aren't futuristic. They're already here." MIT Technology Review, July 28, 2018.
[7] Smolenky 2015, "CRISPR/Cas9 and Germline Modification: New Difficulties in Obtaining Informed Consent, *American Journal of Bioethics* 15(12).
[8] Evitt et al 2015, "Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework," *American Journal of Bioethics* 15(12).
[9] John Harris 2015, "Germline Manipulation and Our Future Worlds," *American Journal of Bioethics*, 15(12).
[10] Baltimore et al 2015, "A prudent path forward for genomic engineering and germline gene modification," *Science* 348(6230).
[11] Ormond et al 2017, "Human Germline Genome Editing," *American Journal of Human Genetics* 101(2).

> (i) quality of life of affected individuals; (ii) safety; (iii) effectiveness; (iv) existence of a clinical need or alternative; (v) costs; (vi) homo sapiens as a species (i.e. relating to effects on our species); (vii) social justice; (viii) potential for misuse; (ix) special interests exercising influence; (x) parental rights and duties; (xi) comparability to acceptable processes; (xii) rights of the unborn child; and (xiii) human life and dignity.[12]

Evitt et al (2015) consider four approaches towards CGET oversight: international ban, temporary moratorium, regulation, and laissez-faire. In their view,

> A complete ban or temporary moratorium will be nearly impossible to enforce due to the low cost of CRISPR and heterogeneity of regional ethical codes. On the other hand, a laissez-faire approach creates risk that research will be conducted before ethical due diligence. Thus, regulation appears to be the most feasible policy.

However, regulations differ across countries. Some countries have banned germline modifications on humans while in others the law is ambiguous or silent.[13] Firms, research consortia, and individual researchers operating in the latter countries must decide along which lines to act, and what type of research to do. Should they altogether avoid (as if under a ban) human embryonic germline modification research? Should they endorse the moratorium and wait until a consensus develops? Should they try to abide by what they can anticipate the ethical regulation might be? Or, should they act as if laissez faire were the morally right approach? There is much at stake in terms of potential discovery, potential mistakes, and the potential to cause a backlash that ends up stifling research.

CRISPR babies

In late November, 2018, an announcement at a genetics conference in Hong Kong shook the world. Dr. He Jiankui, a researcher at the Southern University of Science and Technology in Shenzhen, China, announced the birth of the first gene-edited babies: non-identical twin sisters. When they were still embryos in vitro, Dr. He had used the CRISPR-Cas9 system to try to replace the CCR5 gene with a naturally occurring CCR5-32 mutation that confers immunity to

[12] "The ethics of clinical applications of germline genome modification: a systematic review of reasons." *Human Reproduction* 33(9).

[13] "Many countries do not have explicit legislation in place permitting or forbidding genetic engineering in humans — considering such research experimental and not therapeutic (see go.nature.com/uvthmu). However, in nations with policies regarding inheritable genetic modification, it has been prohibited by law or by measures having the force of law. This consensus is most visible in western Europe, where 15 of 22 nations prohibit the modification of the germ line. Although the United States has not officially prohibited germline modification, the US National Institutes of Health's Recombinant DNA Advisory Committee explicitly states that it "will not at present entertain proposals for germ line alterations." (Lanphier et al 2015, Don't edit the human germ line, *Nature* 519(7544).)

HIV.[14] Dr. He stated that the research followed experiments with animals, and that parents—one of whom was HIV positive—had agreed to the procedure.[15]

Numerous observers first doubted the very existence of the babies, while others called into question the safety of the procedure. Several high-profile scientists considered the pursuit of this pregnancy extremely risky.[16] Reportedly, Dr. He viewed himself as a researcher-entrepreneur and had plans to offer "designer-baby" services for wealthy clients.[17,18] Shortly after Dr. He's presentation, websites of the Chinese government praising Dr. He's accomplishments went down, and announcements were made that his experiments were on hold. The researcher came under heavy criticism and was placed under investigation. Were all these reactions appropriate, or dictated by short-sighted moralism? This might depend on what approach to CRISPR innovation and policy is ethically robust.

Epilogue

Dr. He was later fired by the university[19] and eventually fined and sentenced to prison for "illegal medical practice" in Shenzhen.[20] He has been recently released.

QUESTIONS

If you can answer these questions, you will also be able to understand and critically examine the latest bioethics literature on the subject.

1. Consider yourself in the situation of Dr. He a few years back, contemplating whether to do the research resulting in the "twin CRISPR babies." Who are the actors relevant to the situation, and what are the possible paths of action available?
2. Now elaborate a "values scorecard" for the different paths this doctor may have had available when deciding to do his research.
3. The analysis in (2) should offer some insight on the global conversation about the ethics of gene editing. Which of the four alternatives (or refinement or combination thereof) mentioned by Evitt et al (2015) would you support, and why?

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[14] Michael Le Page, CRISPR babies: more details on the experiment that shocked the world, *New Scientist*, November 28, 2018.
[15] In the absence of the gene surgery, the babies would still not have been born HIV positive because sperm-washing techniques are used to eliminate the virus from sperm before fertilization of the egg.
[16] David Cyranoski, *Nature News*, November 30 2018.
[17] Antonio Regalado, "Disgraced CRISPR scientist had plans to start a designer-baby business." MIT Technology Review August 1, 2019 (https://www.technologyreview.com/2019/08/01/133932/crispr-baby-maker-explored-starting-a-business-in-designer-baby-tourism/, accessed 04/21/22).
[18] Jon Cohen, "The untold story of the 'circle of trust' behind the world's first gene-edited babies." *Science*, August 1, 2019. (https://www.science.org/content/article/untold-story-circle-trust-behind-world-s-first-gene-edited-babies, accessed 04,21/22).
[19] Reuters: https://www.reuters.com/article/us-china-health-babies-idUKKCN1PF0RA (accessed 04/21/22).
[20] David Cyranoski, "What CRISPR-baby prison sentences mean for research." Nature News, January 3, 2020. (https://www.nature.com/articles/d41586-020-00001-y, accessed 4/21/22).