Gene editing on human embryos would not create ‘designer babies’

Would you edit the genome of your future to child? For many people, the initial impulse might lead you to say no, based on the idea that any benefits could be outweighed by the risks. But considering certain classes of genetic conditions, it’s possible that one’s perspective might change.

It has been almost four years since researchers first demonstrated that clustered regularly-interspaced short palindromic repeats and associated an endonuclease (together known as the CRSPR/CAS system) could be used for genome editing. Since that time media discussions of the prospect of utilizing these tools to edit the genomes of human embryos have been influenced heavily by the idea that we should hold off on “designer babies.” Critics suggest that it’s too dangerous; the human genome and gene expression is extremely complex such that meddling could lead to unpredictable consequences.

Despite these concerns, researchers are moving forward with attempts to make edits to human embryos using CRISPR and other genome editing techniques. On February 1, regulators in the United Kingdom announced they would allow these times of edits to be done by scientists at the Francis Crick Institute in London. The goal of this research is to learn more about the early stages of human life and will not involved implantable embryos. But many are beginning to wonder not *if* human embryonic genome editing on implantable embryos, which could produce heritable changes to the genome, but *when* will it happen. However, recent examples suggest that if they do occur the edits may not be as drastic as some are concerned they will be.

Chinese researchers already accomplished editing of human embryo

Based on a cautious perspective, Chinese researchers received strong criticism from around the planet last year for demonstrating that they could edit genomes of 86 human zygotes, even though the zygotes used were not viable. There was no chance that they’d ever be used in a pregnancies going to term, so arguably there was no ethical issue. Published in the journal *Protein and Cell*, the Chinese study was a scientific success. The researchers showed that they could replace a defective DNA sequence causing beta-thalassemia. Theoretically, doing the same thing in viable embryos would result in a cure for such a recessive disease. If taken to term, such an embryo would produce a child with normal hemoglobin, despite having received defective genes from both parents.

Of course, there are other ways to prevent birth of a child with a recessive disease. If an embryo can be tested in the first place to reveal two defective copies of the gene for the hemoglobin beta chain in the first place, then the same embryo can be discarded and the parents can try for a new embryo. After all, two carriers of the mutation have only a 25 percent chance of producing such an diseased embryo. Surely, say critics, screening and discarding embryos is less risky than meddling with an embryonic genome.

That may be a reasonable position, but the Chinese study was still a remarkable accomplishment scientifically. It has potential clinical benefits that should have figured prominently in media coverage, but weren't. On the normally progressive NPR, for instance, coverage was skewed in favor of geneticsexperts who spoke only of the dangers.

"No researcher should have the moral warrant to flout the globally widespread policy agreement against modifying the human germline," said Marcy Darnovsky of the Center for Genetics and Society, for instance, in a quote highlighted by the NPR story. "This paper demonstrates the enormous safety risks that any such attempt would entail, and underlines the urgency of working to forestall other such efforts. The social dangers of creating genetically modified human beings cannot be overstated."

Another expert cited in the story, George Daley of Harvard, said "We should brace for a wave of these papers, and I worry that if one is published with a more positive spin, it might prompt some [in vitro fertilization] clinics to start practicing it, which in my opinion would be grossly premature and dangerous."

The NPR story did not balance such warnings with an appreciation for the potential of such research to lead to life saving therapies, even far into the future. Moreover, media have been taking a similar approach to the topic over the last two years, as if there were no experts to quote who could provide a less alarmist perspective, but such experts do exist.

CRSPR/CAS game changer in biomedicine: Are stories about designer babies missing the boat?

The Chinese embryonic editing study notwithstanding, genome editing technology is currently being used and envisioned for a host of applications less ambitious than embryo tampering, but exciting for biomedicine nevertheless. Beyond numerous research applications that are helping molecular biologists to discover new drugs and other interventions, CRISPR technology is also being studied for modifying stem cells that can be used for all sorts of treatments. It also will be used in vivo in adult humans, probably first in blood conditions since *in vivo* (as well as *in vitro*) modification of blood cells is inherently much easier than than editing sequences within cells of solid tissues. Compared with these applications, the prospect of using embryonic modification clinically lies further into the future, making media coverage focussing on human embryonic modification appear premature.

Early gene editing of embryos would not make major changes

Nobody is arguing today that gene editing technology for human embryos is ready for clinical applications; in fact, several scientists who work with the technology are calling for a moratorium on CLINICAL USE of its embryonic applications. This camp includes co-discoverer of CRISPR/CAS-9 (the particular CRISPR/CAS that occurs naturally in the bacterial species *Streptococcus pyogenes*) Jennifer Doudna of the University of California at Berkeley, who in a recent presentation made a strong case for continuing research that she thinks ultimately will lead to genetically modified human embryos, but holding off on actual clinical implementation of findings until we know more. To explain that this would not amount to an alarmist, anti-progressive approach to biotechnology, Doudna points out that a similar ban implemented during the 1970s in connection with molecular cloning, but the ban was designed to allow laboratory

research to proceed so that we could gain an better understanding of the safety of the technology before using it for making products that would be used clinically (such as genetically engineered insulin for example).

[youtube https://www.youtube.com/watch?v=SuAxDVBt7kQ]
As for calls for a moratorium even on research (which would include human embryos that are not viable like those used in the Chinese study), there are people who can make a good case against going to such lengths. As far back as 2013, before the Chinese study, *Intelligence Squared* hosted a debate in which Nita Farahany, professor of Law and Genome Sciences and policy at Duke, and Lee Silver, professor of molecular biology at Princeton, took a position against a moratorium. They won, at least in terms of being able to change more minds than the team that argued in favor of prohibiting further gene editing work on human embryos.

Farahany and Silver were able to win based on the idea that in the years to come embryonic editing would not be carried out principally to develop new kinds of human beings, the kind of scenario that worries bioethics experts who speak about the “social dangers” of modifying humans. Rather, their point was that goals of embryonic editing would be modest at least in the foreseeable future.

Indeed, Farahany made the point that recent successes in mitochondrial transfer (where a donor gives mitochondria to an embryo) is in fact a category of embryonic genome editing. Future work involving editing of a small number of genes of the human nuclear genome in embryos could then be as a more ambitious project but not different fundamentally from intervening with an embryo’s mitochondrial genome.

In contrast to most of the human genome which is located in the cell nucleus, mitochondrial genes are sequences of DNA that is located in energy producing organelles, mitochondria. that are dispersed throughout the cell cytoplasm, outside of the nucleus. Mitochondria contain their own DNA, because their ancestors are thought to have been independent microorganisms. A human being inherits mitochondria only from his or her mother. In rare circumstances, mitochondria are defective. This can make all of a woman’s eggs defective, but with mitochondrial transfer her nuclear genome can be used for in vitro fertilization with a man’s sperm and her mitochondria–along with the mitochondrial genes–replaced with those from a female donor. Essentially, this gives the off spring two mothers and one father, but importantly normally functioning mitochondria.

Mitochondrial transfer amounts to a major editing job on what becomes an embryo, yet it has led to the birth of apparently normal children. Those children and their parents must live with an uncertainly; it is not possible to be 100 percent sure that the procedure has no long-term consequences. But the children would have been extremely sick without it, or never could have been born at all. This must be taken into account alongside the fact that there are also uncertainties when children are born the natural way.

Editing the nuclear genome

If mitochondrial genome transfer is less ambitious type of embryonic gene editing than manipulation of the nuclear genome, what then is an example nuclear gene editing that could make sense clinically given the current state of biotechnology?

One example might be a case of a monogenetic disease that is detected in an embryo that a parent is not willing to discard, namely one that has already produced a pregnancy. Although currently embryonic gene editing involves making changes to embryos *in vitro*, eventually it should be possible to utilize CRISPR/CAS or other molecular tools that are sometimes known as “DNA scissors.” There are numerous recessive diseases resulting from a child receiving two defective copies of a gene, one from each parent. Beta-thalassemia is one example; another is Tay Sachs disease. While genetic counseling can reduce the incidence of this type of condition, Tay Sachs is seen more often among ultra-orthodox Jews who marry within a small community. Thus, we can imagine a scenario in which it is detected in utero following normal fertilization (as opposed to IVF) and the parents prefer gene editing to abortion. This situation may be rare, but it could create a pathway to bring embryonic gene editing into clinical use.

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