Gene Editing Sperm and Eggs (not Embryos): Does it Make a Legal or Ethical Difference?

Health Policy Portal

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Heritable, human genome editing constitutes one of the most contentious issues facing science policy. This was starkly illustrated by Dr. He's unsafe, unethical, and irresponsible editing of twin girls' embryos in an attempt to confer HIV immunity. The hubris of those experiments stands in contrast to calls for a regulated pathway from the U.S.'s National Academies and the U.K.'s Nuffield Council.[1] But in all of the public discussion of the topic, the focus has been on editing embryos. What about editing sperm or eggs?

Weighed down by technical, statutory, as well as sectarian challenges, the prospect of editing a human embryo's genome at fertilization still remains a long-term goal. Mindful of this reality, the 2015 International Summit on Human Gene Editing reported the editing of mouse spermatogonial stem cells followed by testicular transplantation, resulting in the repair of a cataract-causing mutation.[2] Further experimental work in this area, however, has proven limited. Similarly limited efforts have characterized editing eggs, although the editing of gametes is likely to flourish as the prospect of stem cell-derived gametes becomes reality. This outcome is bound to shift the focus from genome editing the embryo to its antecedent gametes. This will likely increase control of the genome editing process, including eliminating problems of embryonic mosaicism. In this paper we discuss how the editing of sperm and eggs differs from embryos from a bioethical and U.S. legal perspective.

Ethical Differences

Some of the ethical concerns raised about editing embryos are applicable to editing sperm and eggs; others are not. Objections to embryonic gene editing due to the need to destroy human embryos in research and clinical applications — a policy embedded into U.S. law through the Dickey-Wicker Amendment — are quite different for sperm and eggs. Those who have opposed the destruction of embryos, including members of some religious communities have not raised similar objections as to sperm and eggs. Proponents of personhood claims emphasize that "the genetic code of the early embryo is set at the time when sperm and egg form a zygote."[3] But sperm and egg-editing occurs before that moment, upending the claim that editing alters "a person." The activity is more like selecting a sperm or an egg donor.

For those who are concerned with departing from "Nature," or harbor fears over "playing G-d," perhaps editing even at this early stage is problematic. That said, such concerns might be managed by imposing the restriction endorsed by the National Academies that editing should currently be limited "to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects."[4]

About This Column

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That recommendation and others for a regulated pathway might also somewhat allay safety concerns, a set of concerns applicable to editing embryos, sperm, and eggs.

Legal Differences

The main statute that prohibits the clinical use of heritable genome editing is a Congressional appropriations rider, first put into law in 2015 and annually renewed. The rider, provides

> None of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under [the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act] in research in which a human embryo is intentionally created or modified to include a heritable genetic modification[5]

The rider was initially — and surreptitiously — entered into the appropriations bill with little discussion. This past year, the language was briefly removed, prompting a brief debate about whether it applied to mitochondrial replacement therapies and ought to be re-inserted. But the debate firmly centered on the editing of *embryos*. No legislator has considered whether the language applies to the editing of sperm and eggs.

There are strong arguments to be made that the plain text of the rider does *not* apply to sperm and eggs. The rider is narrowly drawn, prohibiting only the government funding of the FDA to engage in two, specific, and bureaucratic activities: *notifying* applicants regarding exemption requests to the agency's IND requirements; or *acknowledging* the receipt of any such requests. These prohibitions apply only "in research" with one of two results: either where a "human embryo is intentionally *created*" or research where "a human embryo is *modified* to include a heritable genetic modification." In either case, the object of the research in the text is a "human embryo," not its antecedent gametes. Further, the language of the rider couches its prohibitions in terms of specific results: those where a human embryo has been either *created* or *modified* — notable uses of the past participle.

By its own terms, the rider does not therefore apply to cases where embryos are not created, such as the mere editing of eggs or sperm without a subsequent act of fertilization. Such an activity neither works on the object of the rider — the human embryo — nor fulfills its result. And even in cases where edited eggs or sperm are eventually used to create an embryo, it can hardly be said that the *embryo* has been modified. The embryo, in such a case, contains the genetic makeup it happens to contain — again, like choosing a sperm or egg donor. The act of fertilization does not *modify* an embryo. Furthermore, any exemption would be filed — that is, when lawyers deliver papers to FDA — concurrently with the editing of the target gametes, before any embryos would have been yet created, let alone modified. And indeed, if such gametes do not end up being used in fertilization, they can hardly be said to have "created" or "modified" any embryos at all.

This plain-text reading aside, one hypothetical further presses the oddness of reading the rider as applying to editing sperm or eggs, pre-fertilization: Imagine an individual, the product of genome-editing, possesses a heritable, edited trait and seeks to reproduce. If the rider applies to using edited sperm or eggs to produce an embryo, it would seem to suggest that their reproductive act falls under the rider — and that they ought to seek an IND from FDA, which the agency must deny acknowledging. It seems unlikely this is what Congress intended.

If the language is clear, that is the end of the matter; Congress' intent — even if contrary to the text — takes a backseat. If, by contrast, the language of the rider is ambiguous, then ordinarily, courts defer to an agency's reasonable interpretation of a provision. So could the FDA clear up the ambiguity on its own? It is unlikely. That deference is only owed when Congress delegates authority to an agency to make rules "carrying the force of law" — and some judges have suggested this may not apply to appropriations riders, including in a similar case pertaining to the Dickey-Wicker Amendment.[6]

Conclusion

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If the appropriations rider does not to apply to editing sperm and eggs, then the next step will depend on the bioethical distinctions drawn above. For those who believe that editing sperm and eggs is just as problematic as embryos, they should seek to alter the rider to make it apply to sperm and egg-editing as well. For those who think that there are important differences, this may open an opportunity to develop a different regulated pathway as to sperm and egg-editing. The path chosen will impact the science, ethics, and financing of genome editing for decades to come.

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Note

Professors Cohen and Sherkow declare no conflict of interest. Professor Adashi is co-chair of the Safety Panel of Ohana Biosciences, Inc. (Cambridge, MA).

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