

Letter to the Editor

Gene Editing Sperm and Eggs for Use in Clinical Trials

In the Fall 2020 issue of the *Journal of Law, Medicine & Ethics*, Professors Cohen, Sherkow, and Adashi (authors) address an annual appropriations rider that bars the U.S. Food and Drug Administration (FDA) from acknowledging receipt of applications for clinical trials in which a human embryo is intentionally created or modified to include a heritable genetic modification.¹ They recognize that the rider affects applications for clinical trials in which human embryos are modified directly and transferred to women to initiate a pregnancy. However, they suggest the rider does not apply to applications for clinical trials in which scientists attempt to get women pregnant with edited sperm and eggs. With due respect, I believe their interpretation is incorrect.

The FDA regulates clinical trials in which drugs or biological products are administered to human subjects.² In 2001, the Director of its Center for Biologics Evaluation and Research asserted that the FDA has jurisdiction over assisted reproductive technologies in which genetic material is transferred other than by union of gamete nuclei. She gave examples, including “genetic material contained in a genetic vector, transferred into *gametes* or other cells” (emphasis added).³ As one would expect, the Director did not foresee or address CRISPR/Cas9, base editing, and other current molecular tools specifically. In 2017, however, the National Academies acknowledged that the FDA has jurisdiction over clinical trials in which scientists attempt to get women pregnant with edited sperm and eggs.⁴

The authors do not dispute FDA jurisdiction as such. However, they argue that the rider does not apply if edited gametes are used to create an embryo. In their view, an embryo created via fertilization simply contains the genes of its constituent gametes; thus, it does not include a heritable genetic *modification* as the rider requires.⁵

A common legal maxim holds that all words of a statute should be given effect if possible.⁶ The rider applies when a human embryo is intentionally *created or modified* to include a heritable genetic modification. In adopting this language, Congress evidently intended the rider to cover two distinct acts: creation *or* modification. However, the authors write “creation”

out of the rider by positing that an embryo constituted with edited gametes can never include a heritable genetic modification.

An alternative interpretation that gives effect to all words of the rider is possible. This column will provide an illustration; but first, some scientific background may be helpful. The reader may have heard of cats that glow green in the dark. These animals result from experiments in which scientists add the green fluorescent protein (GFP) gene to cat eggs before fertilizing them and transferring them to surrogate mothers. The resulting kittens glow green, and so do their own offspring.⁷ Thus, the cat eggs include a genetic modification. The embryos created from the eggs also include that genetic modification, which is heritable.

Now, suppose a scientist wishes to conduct a similar experiment with human subjects. She plans to add the GFP gene to human eggs, which then will contain a *genetic modification*. The scientist will fertilize the eggs with sperm — thereby intentionally *creating* human embryos that *include* the original genetic modification — and transfer those embryos to women for gestation. If the experiment succeeds, the end result will be babies who glow in the dark and can pass that trait down to their own offspring. In other words, the genetic modification will be *heritable*. Can the FDA acknowledge receipt of her application to conduct a clinical trial? The answer should be no: the elements of the rider are satisfied. Moreover, although legislative history is sparse, logic supports this outcome. If Congress was worried about heritable genetic modifications, it would attempt to pause all such experiments, whether the genes in question were modified at the gamete or embryo stage.

This is not to say that the rider is a good thing. It serves no legitimate scientific purpose. If Congress eliminated it, the FDA could receive and consider applications for clinical trials in which scientists corrected deadly mutations in gametes or embryos and provided them to women for reproductive purposes. Of course, the FDA would not permit clinical trials to proceed until and unless proponents could demonstrate that the technology was safe and effective for participants, including the children-to-be.⁸

The real purpose of the rider is political. It allows Congress to duck the issue of heritable human genome editing without having to engage the ethical and social questions involved. This act of political cowardice

comes at the price of scientific advancement and medical treatments for carriers of genetic mutations and their children.

I share the authors' frustration with the rider. Unfortunately, I do not agree that scientists can sidestep it by working with gametes rather than embryos. Instead, scientists should lobby Congress to eliminate the rider so that the FDA can do its job.

Kerry Lynn Macintosh

Inez Mabie Distinguished Professor of Law,
Santa Clara University School of Law
kmacintosh@scu.edu

References

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P.R. Romano, and J. Almqvist, eds., *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (Cambridge, England: Cambridge University Press, 2019): 103–128, at 109.

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6. *United States v. Menasche*, 348 U.S. 528, 538–39 (1955).
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8. K.L. Macintosh, *Enhanced Beings: Human Germline Modification and the Law* (Cambridge, England: Cambridge University Press, 2018): at 125

The Authors Respond

Dear Editor,

We thank Prof. Macintosh for her thoughtful reading of our article, but we respectfully disagree with her interpretation of the rider. Prof. Macintosh's interpretation, which centers on giving effect to the words "created or modified," elides the *object* of such actions: "a human embryo." As we explain in our article, an embryo does not exist until it is "conceived" by the union of sperm and eggs, therefore, whatever "heritable genetic modi-

fications" the rider seeks to enjoin must occur *after* this critical moment. For that reason, among others, we believe our interpretation of the rider is correct. We nonetheless share Prof. Macintosh's remaining concerns about the rider and note that while Congress may — or may not — choose to re-establish or clarify this section in its ongoing budget, the technological and interpretive gap we identify remains in place.

*I. Glenn Cohen,
Jacob S. Sherkow,
and Eli Y. Adashi*