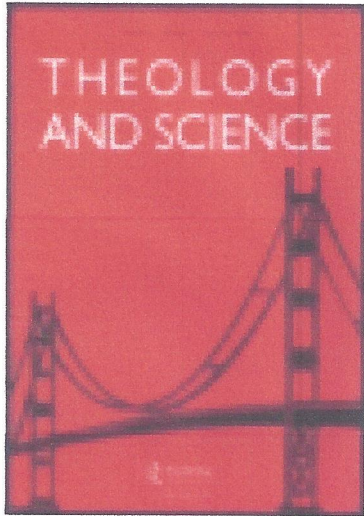


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CRISPR, the Precautionary Principle, and Bioethics

TED PETERS

Here is the question scientists and their bioethicist friends are asking: *Should we modify the germline in human beings (and animals too)?*

On most days when such questions arise, the average bioethicist can get by with a single-word vocabulary. All he or she needs to do is pronounce the word “No,” with emphasis, and the job is done.

If a bioethicist were to say, “Yes” too often, he or she would be shunned by colleagues as having sold out to the industry.

Let’s try this on for size: “Yes, but not yet.” That’s a long sentence. Perhaps it should be reserved for ethical issues deserving of its complexity.

I think “Yes, but not yet” might be the most appropriate ethical counsel we could offer to those geneticists embroiled in the CRISPR controversy. During the era of the Human Genome Project in the 1990s, this was called “germline modification” or “human inheritable genetic modification.” Today, it’s called “gene editing.” Regardless of the name, what we are talking about is altering the genetic code in germ cells—in eggs or sperm—that will influence future generations of a given species.

Scientifically and ethically, this sounds like a great idea. Suppose we would snip out of the germline the gene for Huntington’s disease located on the short arm of chromosome 4. Huntington’s is a neurodegenerative disorder leading to mental decline, dementia, uncontrollable body movements, anxiety, depression, and aggression. In 1993, Huntington’s was traced to a mutation leading to a trinucleotide repeat—that is, three DNA bases (cytosine-adenine-guanine, or CAG) get repeated multiple times (... CAGCAGCAG ...). So, looking at this, it is reasonable to ask: Should we snip out this allele from the germ cells, so that all children born later will be free of the Huntington’s gene? In fact, if scientists do this systematically, we might eliminate Huntington’s disease from the human gene pool. And, further, if scientists should perform this task for, say, another 2000 genetically based diseases, then ... what?

Two decades ago, the bioethicists said, “Whoah!” Why? Are the bioethicists heartless? Do bioethicists want to see Huntington’s patients suffer? No, that is not the reason. Their judgment was based on what we don’t know. What we don’t know is the long-term effect of such large-scale changes in the genome. Genes work with other genes and other DNA in delicate systems like Swiss watches, mutually influencing one another; so, to eliminate one set of gears in

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the Swiss watch might disaggregate the entire system beyond repair. This could happen without our knowledge.

Anticipating such an unpredictable disaster led bioethicists to invoke the Precautionary Principle. The so-called *Wingspread Definition* of the *Precautionary Principle* was formulated at the 1992 United Nations Conference on Environment and Development: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of the process or product, rather than the public, should bear the burden of proof." Although the Precautionary Principle applied originally to ecological ethics, it seemed to bioethicists that it might apply equally well to genetics.

In short, when today's scientists engage in therapies that might yield consequences for generations to come, the burden of proof regarding safety must be borne now. Rather than march forward and risk falling off a cliff, the burden of proof requires that we locate all the cliffs before marching. So, the considered judgment of bioethicists was this: "Yes, but not yet."

Now, two decades later, the concern is erupting once again due to CRISPR/Cas9 and laboratory success at gene editing in both animals and humans. CRISPR is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats.

Gene-editing techniques have been using enzymes called nucleases to snip DNA at specific points and then delete or rewrite the genetic information at those locations. Developed in China,¹ the technique called CRISPR/Cas9 is particularly easy to use and is spreading rapidly to new laboratories around the world. Current applications of the technology are in somatic—not germline—cells. For example, Sangamo BioSciences of Richmond, California, has used zinc-finger nucleases, an older gene-editing technology, to remove a gene from white blood cells that encodes the receptor to which HIV binds to enter the cells. Application to germline modification is just around the corner.

CRISPR is already migrating out of the public university and taking up residence in entrepreneurial enterprises. Feng Shang of MIT has founded Editas Medicine to develop and sell CRISPR-created therapies. Instead of taking prescription pills to treat their ailments, patients may one day opt for genetic surgery. By using an innovative gene-editing technology, the surgeon will snip out harmful mutations and swap in healthy DNA.²

Scientists are buzzing about ethical concerns, concerns over safety, and bio-security. One concern is that nucleases could make mutations at locations other than those targeted, potentially causing disease.³ As a precaution, more research will be required before letting the gene-editing technique loose to wander the world's laboratories and businesses.

Some concerned scientists, led by Edward Lanphier, president of Sangamo and chairman of the Alliance for Regenerative Medicine in Washington DC, speak out:

In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could

hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited.⁴

Note that the scientists provide two reasons for precaution. First, unpredictable consequences risk negative impact. This warrants appeal to the Precautionary Principle. All well and good.

Second, scientists want to avoid offending the public who might shut off the supply of their research money for non-germline research. Just to be certain you get the point, look at what else they say:

Key to all discussion and future research is making a clear distinction between genome editing in somatic cells and in germ cells. A voluntary moratorium in the scientific community could be an effective way to discourage human germline modification and raise public awareness of the difference between these two techniques. Legitimate concerns regarding the safety and ethical impacts of germline editing must not impede the significant progress being made in the clinical development of approaches to potentially cure serious debilitating diseases.⁵

The other creatures with whom we humans share our planet have also become an ethical concern. Jeantine Lunshof at the University of Groningen in the Netherlands, for example, invokes precaution regarding the possible environmental impact of removing from mosquitoes the capacity to spread malaria. In combination with another technique called *gene drive*, CRISPR has been used successfully to modify mosquitoes and the fruit fly:

Designer babies and precision gene therapy should not blind us to the much more pressing problem: the increasing use of CRISPR to edit the genomes of wild animal populations. Unless properly regulated and contained, this research has the potential to rapidly alter our ecosystems in irreversible and damaging ways.⁶

Finally, then, we must ask: what's a bioethicist to do? I offer three recommendations.

First, find some scientists who will listen. It appears that many laboratory researchers are ready to listen. Well, not exactly. They are ready to speak. They are already speaking out on ethical issues raised by germline editing. We in the public sector should welcome this, to be sure; but we should keep our skeptical ears open. Do our ethically minded scientists register authentic moral concern over biosafety and environmental safety? Or, are they more invested in *appearing* to be ethical so as to keep public research funds flowing?

Second, we should applaud the willingness within the scientific community to give serious consideration to the Precautionary Principle. Prudence, rather than Prometheanism, should be our watchword here. If the public is willing to threaten to withhold research money for genetic therapies, then researchers might become even more cautious regarding germline editing. Such a fiscal threat would have no impact on private business selling CRISPR-based services, however.

Third, ethicists and the supporting public should promote increased research into prognosticating the future impact on the environment and the wider ecosystem. Looking ahead is indispensable. Yet, we must acknowledge what can

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and cannot be done. We cannot predict the future with precision. This suggests that at some point we may decide to gamble on the most beneficent future we can envision.

To relieve future generations of Huntington's disease or malaria infection ranks so high on our scale of values that we cannot dismiss these opportunities lightly. The bioethical principle of beneficence—to facilitate improved health and well-being wherever the opportunity arises—encourages the research community to press forward, to develop these life-saving technologies.⁷ When evidence suggests that harm could result from proceeding, then we should invoke the non-maleficence principle and avoid doing harm. The Precautionary Principle is a variation on the non-maleficence principle, because it opens a temporal space to explore the possibilities of doing harm. But, exploring possibilities cannot go on indefinitely. At some point, researchers need to leap forward. The Precautionary Principle should be a temporary principle, whereas the Beneficence Principle should be permanent.

Fourthly and finally, the bioethicist should stutter loudly, "Yes, but not yet."

Notes

- 1 David Cyranoski and Sara Reardon, "Chinese Scientists Genetically Modify Human Embryos," *Nature* 521:123 (2015); "Rumours of Germline Modification Prove True—And Look Set to Reignite an Ethical Debate," <http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378>.
- 2 Helen Shen, "CRISPR Technology Leaps from Lab to Industry," *Nature* (December 3, 2013), <http://www.nature.com/news/crispr-technology-leaps-from-lab-to-industry-1.14299>.
- 3 "To date, a serious knowledge gap remains in our understanding of DNA repair mechanisms in human early embryos, and in the efficiency and potential off-target effects of using technologies such as CRISPR/Cas9 in human pre-implantation embryos." Puping Liang et al., "CRISPR/Cas9-Mediated Gene Editing in Human Trippronuclear Zygotes," *Protein and Cell* 6:5 (2015), 363–372, 363.
- 4 Edward Lamphier, Fyodor Urnov, Sarah Ehlen Haecker, Michael Werner, and Joanna Smolenski, "Don't Edit the Human Germ Line," *Nature* 521:117 (2015), <http://www.nature.com/news/don-t-edit-the-human-germline-1.17111>. See David Baltimore et al., "Biotechnology: A Prudent Path Forward for Genomic Engineering and Germline Gene Modification," *Science* 348:6230 (2015), 36–38.
- 5 Lamphier et al., "Don't Edit the Human Germ Line."
- 6 Jeantine Lunshof, "Regulate Gene Editing in Wild Animals," *Nature* 521:127 (2015), 127.
- 7 "[O]ne must discern the strength of each ethical principle—non-maleficence and beneficence—and weigh them given particular circumstances. ... In circumstances where great harm can be proven, non-maleficence will be overriding. But in the absence of proven and substantial harm, beneficence will be overriding." Ted Peters, Karen Lebacqz, and Gaymon Bennett, *Sacred Cells? Why Christians Should Support Stem Cell Research* (New York: Rowman & Littlefield, 2008), 78. Here I, along with my bioethical colleagues, invoke precaution; but we place the burden of proof on the non-maleficence side.