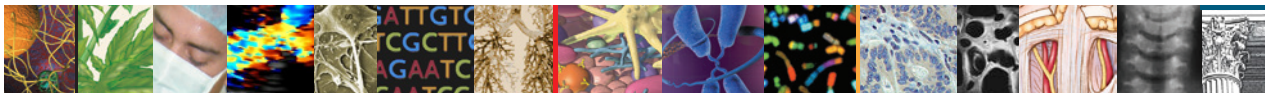

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Perspective

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Compelling Reasons for Repairing Human Germlines

George Church, Ph.D.

Under normal circumstances, if you combined sperm half of which carried a dominant disease allele with unaffected oocytes, only 50% of the resulting human embryos would be expected to have unaffected copies of the gene in question. Researchers Ma, Mitalipov, and colleagues recently reported that using the germline-editing technology CRISPR (clustered interspaced short palindromic repeats)-Cas9, they were able to increase that proportion to 72%.[1] Notably, the goal was "precise gene editing," not merely targeted damage to a gene. The need for data to rule out alternative explanations — parthenogenesis or deletions affecting the polymerase-chain-reaction primers — has been noted.[2]

The new work involved at least three changes from previous embryo gene-editing efforts: using a nuclease designed to cut only the disease-causing version of a gene while avoiding the normal chromosome; providing that nuclease in protein form rather than DNA form (intended to reduce off-target damage); and including it as part of intracytoplasmic sperm injection before the sperm chromosomes duplicate (to reduce the likelihood of mosaic mixtures within embryos). The synthetic DNA intended to correct the sperm's mutation was marked with two nucleotide changes but was not found in the final embryos, a finding explained by the authors as the result of repair of the Cas9-cut genome using maternal DNA rather than the synthetic DNA. Nevertheless, one hopes that the researchers checked the haplotypes of the embryo blastomeres to determine whether the maternal copy was indeed copied, rather than the paternal copy's simply being lost.[2]

What might be future steps toward repairing the human germline? In the face of parental or societal concern about embryonic life, it would be best if the fraction of unaffected embryos could be closer to 100%. We can see how to get very close to fully normal embryos through clonal analysis of treated stem cells[3] rather than direct action on embryos — selectively using stem-cell clones found to have no off-target errors, no on-target errors, no errors unrelated to editing (i.e., spontaneous point mutations or chromosome aneuploidy), and no epigenetic errors.

Second, the allele-specific editing of Ma, Mitalipov, and col-

leagues depended on the existence of a big difference between the two alleles — a 4-base-pair deletion. A different strategy might be needed to fix more typical genetic problems involving a single-nucleotide variant (SNV). A major difficulty is that after an SNV is repaired, CRISPR tends to keep cutting the genome until a larger mutation stops it. Alternatives include adeno-associated virus–vectored donor DNA and Perfect-Match TAL editing (deployable at every possible position in the genome, in contrast to Cas9, which is limited to about 9% of the sites in the genome). Another strategy is to introduce adjacent "silent" mutations in the donor DNA to prevent postrepair recleavages. Finally, potential non-nuclease solutions, though more cumbersome to program, avoid the problem of random on-target errors posed by nucleases.

A third improvement would be to reduce risk to embryos by intervening earlier, before sperm are formed.[4] Though it's tempting to dismiss such technology as being limited to a small market or being far off technically, it would be more helpful to prepare thoughtfully for its potential early arrival and broad application, given the pace of development of next-generation sequencing for noninvasive prenatal testing and prenatal genetic screening in conjunction with in vitro fertilization. Of 130 million babies born each year worldwide, roughly 7 million have serious inherited genetic disorders. Even though some of these cases could be averted through noninvasive prenatal testing or prenatal genetic screening, both procedures result in the discarding of embryos, which many people find unacceptable. In 2004, a Vatican commission stated that "Germ line genetic engineering with a therapeutic goal in man would in itself be acceptable . . . in the stem cells that produce a man's sperm, whereby he can beget healthy offspring with his own seed by means of the conjugal act." Studying the acceptability of such an alternative to discarding of embryos in various cultures seems worthwhile.

A June 2015 report from the Congressional Subcommittee on Research and Technology claimed that "an April editorial in Science Magazine called for a prudent path forward for genomic engineering. It recommended a moratorium on further research." The cited article,[5] however, did not include the word "moratorium" (or "ban" or "pause"). Moreover, a recent report by the National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that "germline genome-editing research trials might be permitted, but only following much more research aimed at meeting existing risk/benefit standards for authorizing clinical trials and even then, only for compelling reasons and under strict oversight." The report goes on to list 10 criteria, including "converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health" and "long-term, multigenerational follow-up."

This NASEM recommendation is not fundamentally different from the Food and Drug Administration (FDA) approval process for other new therapies. But the Section 749 rider on the Consolidated Appropriations Act of 2016 undermines the FDA mandate to save lives, in asserting that "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 . . . in research in which a human embryo is intentionally created or modified to include a heritable genetic modification." This prohibition ignores the current medical practice of modifying human genes in would-be parents during cancer chemotherapy. Are such random germline mutations really more acceptable than careful restoration of a verified normal state?

As others have argued, Congress's interfering with the normal FDA investigational new drug application process can put the United States at a competitive disadvantage in what may be the highest-impact technology of the century. But a deeper question is, do we want to lose the moral high ground on what would be a way of reducing abortions and losses of embryos? Do we want legal inertia based on lack of awareness of moral options to force Americans to go abroad to have healthy babies by means of sperm editing? Britain's population has been actively engaged in these topics, and some of the leadership of China have high levels of technical knowledge.

Finally, some critics fret about the slippery slope of human enhancement and the impossibility of obtaining consent from future generations. Doing nothing merely for fear of unknown risks is itself risky — greatly restricting the advance of medicine. It may seem tempting to draw a line for permissible gene editing at some qualitative or quantum step such as "germline versus soma" or "enhancement versus basic health,"

but the reality is that we often regulate practices on the basis of ethical costs and benefits at specified points along a continuum — for example, speed limits, blood alcohol levels, and age limits. We already embrace many enhancements inherited over multiple generations — generally without consulting future grandchildren — for example, education, homes, and extinction of pathogens through the use of vaccinations. The issue for many critics lies not in enhancement relative to our ancestors, but rather relative to one another. We should study cases in which technologies are equitably distributed to all 7.5 billion of us, such as the extinction of smallpox and polio through global enhancement of immunity.

An audio interview with Dr. Church is available at NEJM.org

As we list compelling reasons to repair human DNA (both soma and germline), we include infirmity of our embryos, infertility in adults, and cognitive decline in our oldest citizens. When people aim to restore health, they might justifiably aim slightly higher than average. I believe we should be regulating therapies on the basis of measured outcomes, rather than a priori guesses, just as we should evaluate employees on the basis of their actual performance, rather than poor predictors such as appearance. As we reduce the cost and improve the quality of DNA editing, it is critical to enable diverse conversations and broad education on this topic. It will be important for us to guard against commercial manipulation of perceived medical needs, but not at the cost of preventing the development and use of a whole category of promising preventive medicine.

Disclosure forms provided by the author are available at NEJM.org.

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Designing Ethical Trials of Germline Gene Editing

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The recent announcement that researchers have successfully used the CRISPR (clustered regularly interspaced short palindromic repeats) gene-editing technique to correct a mutation that leads to hypertrophic cardiomyopathy in human embryos is the latest reminder of the urgency of the social and ethical issues surrounding potential clinical use of gene editing.[1] Clinical use in humans is still far off; much research is needed to determine whether germline gene editing can be done safely and with acceptable risks; the legal and regulatory status of the technology varies widely around the world.[2] Nevertheless, the drastic reduction in rates of off-target effects and mosaicism in the recent study — only 2 years since the first such experiment on human embryos was announced — shows how quickly the technology is progressing.

Much of the biomedical ethics literature on gene editing has focused on broad social issues related to how it should be done, such as questions about using it for enhancing human cognitive abilities. Comparatively little has dealt with more ground-floor ethical issues about the design of clinical trials and use of gene editing in reproductive medicine. The time for that discussion has now come: foreseeable use of gene editing in reproductive medicine is no longer science fiction, and it's important to consider seriously what would be required for the conduct of ethically sound clinical trials of this new technology.

Human germline gene editing raises a new set of ethical issues that are extremely difficult to resolve on the basis of current ethical guidelines and regulations. One of the most significant of these issues concerns intergenerational monitoring — long-term