VIEWPOINT

Toward Responsible Human Genome Editing

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Viewpoint

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Progress in genome editing has generated interest because of its promise to improve human health. The development of the RNA-guided CRISPR-Cas9 genome editing system[1] has spurred a remarkable increase in research because this technique is more efficient, less costly, and easier to use than earlier protein-guided technologies such as zinc finger nucleases and TALENs.

The speed at which the science is advancing raises important questions about human genome editing, such as how to balance potential benefits against risks of unintended harms, how to regulate the use of genome editing and incorporate societal values into policy decisions, and how to respect the diverse perspectives of individuals, nations, and cultures that will influence whether and how to use these technologies. A new report from the US National Academies of Sciences and Medicine[2] addresses these questions and makes recommendations for the application and oversight of human genome editing in 3 major settings: (1) basic laboratory research; (2) clinical applications in somatic cells (whose effects would be limited to treated individuals); and (3) future potential clinical applications in germline cells (in which genetic changes would be inherited by future generations).

Basic Research

Basic research using genome editing advances the understanding of gene functions, early human development, stem cells, reproductive biology, links between genes and disease, and the progression of cancers and other diseases with a strong genetic component. Basic research in genome editing is conducted under ethical norms and regulatory frameworks that include local and national oversight committees to ensure laboratory safety and to protect the interests of people who have donated tissues and cells to research. The committee concluded that basic research involving somatic and germline cells is essential to the advancement of science and medicine and recommends that this research should continue under existing regulatory structures.

Somatic Cell Editing for Treatment and Prevention of Disease and Disability

There has been considerable progress in the clinical application of gene therapy to treat diseases,[3] but new genome editing technologies have greatly accelerated progress. For example, a clinical trial was approved by the National Institutes of Health Recombinant DNA Advisory Committee to use CRISPR-Cas9 to modify immune cells to target cancer in patients for whom chemotherapy and other conventional treatments have failed.[4] Somatic cell genome editing is also enabling new applications in the treatment of diseases with a genetic basis, including sickle cell anemia and immunodeficiency diseases.

Clinical applications of genome editing can be conducted ex vivo or in vivo. Ex vivo approaches have technical advantages because gene edits made to cells removed from a patient can be verified by assessing function before returning the cells to the patient. Although technical challenges remain for in vivo editing to achieve effective delivery and avoid off-target events, a trial is already under way for hemophilia B.[5]

Clinical applications of genome editing are included under the umbrella of gene therapy,[3] which has been subject to regulatory oversight and governed by ethical norms since the 1990s. When conducted carefully and with proper oversight, gene therapy research has garnered widespread public support. The committee concluded that clinical trials of genome editing in somatic cells for the treatment or prevention of disease or disability should continue, subject to existing regulatory frameworks.

Potential Use of Genome Editing for "Enhancement"

A controversial aspect of genome editing concerns its potential use for modifying physical traits and capacities beyond those typical of adequate health. For example, using somatic genome editing to improve musculature in patients with muscular dystrophy would be considered a restorative treatment, whereas using the same intervention for individuals with no known pathology and average capabilities would be considered "enhancement." Currently, the potential benefits of applications for enhancement are unlikely to outweigh the risks, and the report recommends that such uses should not be approved at this time. With additional research, risks will probably diminish, and it will become increasingly important to have public engagement and input on how to weigh the purported benefit of any enhancement against risks and to explore the social implications, both real and feared, as governance policies develop. Although one day it may be technically safe to use genome editing for enhancement, societies, professional organizations, and governmental agencies still may choose not to approve such applications because they violate certain core principles such as respect for persons, equity, and fairness. Moreover, it is important to emphasize that many of the traits, such as intelligence, that are commonly discussed in the media as potential targets for enhancement, are complex and thus very unlikely to be readily modified by genome editing.

Germline Editing for Treatment or Prevention of Disease or Disability

A third potential application of human genome editing involves alteration of germline cells to prevent serious disease or disability. Germline editing has been conducted successfully in animals, but major technical

challenges remain in developing the technology for safe and predictable use in humans. Nonetheless, this line of research is of interest because there are thousands of inherited diseases caused by mutations in single genes. When no other reasonable alternatives are available, editing germline cells could reduce the burden of disease for a child and allow prospective parents to have genetically related offspring without the risk of transmitting disease-causing mutations to their children.

Because germline editing would result in genetic changes that could be inherited by the next generation, it raises greater concerns about safety, informed consent, and unintended effects. It has also been argued that germline gene editing crosses an ethical line, and there are concerns about equity of access and the potential effect on individuals with disabilities. Given these technical and societal concerns, the committee concludes that there is need for caution in any move toward germline editing, but that caution does not mean prohibition. The report recommends that clinical trials of germline editing might become permissible but only after much more research to meet appropriate risk/benefit standards for authorizing such trials. Even then, germline editing should be permitted only for compelling reasons and under strict oversight.

In the United States, authorities are currently unable to consider proposals for this clinical research because of a prohibition on use of federal funds by the US Food and Drug Administration to review "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[6] Similar prohibitions exist in many other countries. There is a risk that if established bodies are not permitted to regulate this field, it might develop outside societal norms, leading to applications that are not scientifically valid or that violate core ethical principles. The committee defined a set of stringent criteria under which heritable germline editing might be permissible if US restrictions are lifted or if countries without legal prohibitions proceed with this line of research:

- absence of reasonable alternatives
- restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to a serious disease or condition
- conversion only to gene variants that are prevalent in the population and known not to have adverse effects
- credible preclinical and clinical data on risks and potential health benefits
- ongoing, rigorous oversight during clinical trials
- comprehensive plans for long-term multigenerational follow-up
- continued reassessment of both health and societal benefits and risks, with wide-ranging, ongoing input from the public
- reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

If these criteria cannot be met, then clinical trials should not proceed. The committee also developed a set of principles suitable for use by all countries for establishing the norms and practices to govern human genome editing across its many applications. These principles include promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational cooperation. The committee included members from 4 continents and met with researchers, ethicists, patient advocates, and policy makers from around the world. The recommendations include proposals for ongoing discussion and coordination of the international oversight of human genome editing.

Incorporating Public Engagement Into Regulatory Oversight

The recommendations also urge public education and engagement, which will be crucial in the process of assessing and applying societal values to the risks and benefits of genome editing technologies and the ethical dimensions they involve. For somatic genome editing for treatment of disease, the Recombinant DNA Advisory Committee currently provides a forum for public engagement. While the report recommends against using somatic cell editing for enhancement at present, continued transparent and inclusive public engagement and education through multiple forums are needed to assess whether there is evolution of societal views on this issue over time. With respect to heritable germline editing, broad participation and input by the public, along with ongoing reassessment of both health and societal benefits and risks, should be a precondition for moving any clinical trials forward.

The thrust of the report's recommendations is to maximize the benefits to human health of any applications of genome editing. While heritable germline editing is currently not feasible and probably will not be for several years, it is possible to foresee paths whereby it may become a realistic possibility. It is incumbent on society to take advantage of the opportunity to promote public engagement on the societal issues to inform regulatory decisions if and when that possibility becomes a reality. The committee's recommendations on heritable germline editing constitute a progression from the category of "never" to the category of "maybe, but only if ..." but with no applications for enhancement—the goal would be healthy infants, not "designer babies."

ARTICLE INFORMATION

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