NATIONAL ACADEMY OF SCIENCES AND
NATIONAL ACADEMY OF MEDICINE

REPORT HIGHLIGHTS

HUMAN GENOME EDITING SCIENCE, ETHICS, AND GOVERNANCE

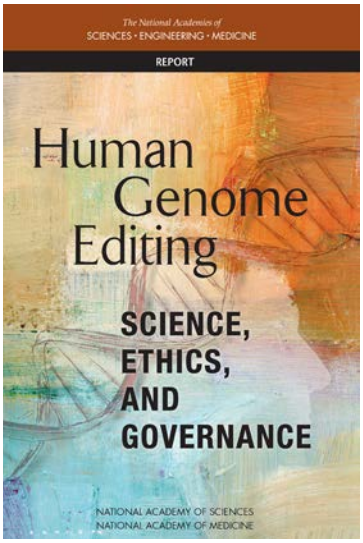
PROGRESS IN GENOME EDITING—technologies for making precise additions, deletions, and alterations to DNA—has generated interest around the globe because of the promise it holds to improve human health. For example, genome editing is being tested in clinical trials to engineer immune cells to target cancerous tumor cells and to make cells more resistant to HIV. Genome editing could also be used to develop new treatments for devastating genetic diseases like Huntington's disease, sickle cell anemia, immune deficiencies, muscular dystrophy, and cystic fibrosis.

As with other medical advances, each new potential use of genome editing carries a unique set of benefits, risks, regulatory issues, and societal implications. Important questions that have been raised about human genome editing include: how to balance potential benefits with the risk of unintended harms; how to govern the use of genome editing; how to incorporate societal values into clinical applications and policy decisions, and how to respect the inevitable differences across nations and cultures that will shape diverse perspectives about whether and how to use these technologies.

Now is the time to consider those questions. This need is pressing, in large part, because of the recent development and growing use of the CRISPR/Cas9 system, first developed as a genome-editing system in 2012. CRISPR/Cas9's accuracy, precision, and ease of use have resulted in an explosion of basic research in genome editing, and clinical trials are already underway testing how this technology can be used to improve health. To help direct appropriate use of genome editing to promote human wellbeing, this report examines the scientific, ethical, and social issues it raises, and assesses the capacity of governance systems to ensure its responsible development and use.

GENOME EDITING APPLICATIONS AND POLICY ISSUES

There are three major settings in which genome editing can be applied in biomedicine: (1) basic research that helps advance understanding of human disease and its treatment; (2) clinical applications to treat or prevent disease or disability in somatic cells (non-reproductive cells), and; (3) clinical applications to treat or prevent disease or disability in germline cells (reproductive cells).



The committee that authored this report based its assessment on a review of the literature and information gathering meetings that included discussions with clinicians, researchers, policymakers, public engagement experts, industry representatives, patient advocates, and the public. The committee also developed a *set of principles* suitable for use by many countries for establishing processes to govern human genome editing that include promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational cooperation.

BOX 1 ABOUT CRISPR/Cas9

CRISPR (clustered regularly interspaced short palindromic repeats) is an acronym that refers to short, repeated segments of DNA that were originally discovered in bacteria. These segments provided the foundation for development of a system that, when paired with other components such as Cas9 (an RNA-guided enzyme that cuts DNA) can be readily programmed to edit specific segments of DNA. Together, CRISPR/Cas9 finds a specific segment of DNA and creates a double-stranded break; cellular DNA repair mechanisms are then used to inactivate or modify the genome in a targeted manner. CRISPR/Cas9 is more efficient, less costly, and easier to use than earlier protein-guided gene editing strategies such as meganucleases, zinc finger nucleases, and TALENS.

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BASIC SCIENCE RESEARCH

Basic biomedical research using genome editing—typically conducted in a laboratory setting—offers significant opportunities to advance human health and medicine. Most basic research to date has used human somatic cell types such as skin, liver, lung, heart cells, and blood but some research also uses germline cells including early-stage human embryos, eggs, sperm, and the cells that give rise to egg and sperm cells. This research is helping to advance understanding of gene functions and arrangements, DNA-repair mechanisms, early human development, the 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 existing ethical norms and regulatory frameworks. These include local and national oversight committees to ensure laboratory safety and to protect the interests of the people who have donated their tissues and cells to basic research. Some basic genome editing research is done with gametes and early embryos in order to gain important insights into human fertility, miscarriages, fetal development, stem cells, and regenerative medicine. This research does not involve transfer of embryos for gestation; it remains entirely within the laboratory and does not involve any heritable changes. Rules governing the funding and permissibility of embryo research vary among countries, reflecting a diversity of views about the embryo. Regulatory oversight and limits in the United States come from existing state embryo research laws or limitations imposed by federal or other funders.

The committee concludes that basic research involving both somatic and germline cells is essential to the advancement of science and should continue with existing regulatory structures.

SOMATIC CELL EDITING FOR TREATMENT AND PREVENTION OF DISEASE AND DISABILITY

A second application of human genome editing involves alteration of somatic cells to treat or prevent disease or disability. One example of this application is a clinical trial that has been approved to program cancer patients' immune cells to target the cancer. This trial focuses on patients in whom chemotherapy and other conventional treatments have failed.

In addition to cancer, somatic cell genome editing holds great promise for treatment of various genetic diseases. Genome editing can be applied outside the body (*ex vivo*) by first removing relevant cells from a person's body (e.g., bone marrow), making specific genetic changes, and then returning the cells to the same individual. Somatic genome editing can also be done in the body (*in vivo*) by injecting a gene-editing tool into the bloodstream or target organ. However, there are still technical challenges in effectively delivering *in vivo* genome editing to get the intended result, and to avoid unintended effects ("off-target" effects). Despite these challenges of *in vivo* editing strategies, clinical trials are already underway for hemophilia B and mucopolysaccharidosis I.

The idea of making genetic changes to somatic cells is not new, and these changes have long been referred to as "gene therapy." Gene therapy has been subject to regulatory oversight and governed by ethical norms since it began in the 1990s, and in general there is public support for this field of research and medicine. The U.S. framework for that oversight applies from the early stages of laboratory research work to preclinical testing, human clinical trials, approval for introduction into medical therapy, and post-approval surveillance.

The committee concludes that clinical trials of genome editing in somatic cells for the treatment or prevention of disease or disability should continue, subject to the ethical norms and regulatory frameworks that have been developed for existing somatic gene therapy research and clinical use to treat or prevent disease and disability. However, because there are a number of ways that somatic genome editing can be done, regulators should consider the technical context of the genome editing system, as well as the proposed clinical application in the process of weighing anticipated risks and benefits. The committee concludes that there is no single standard for somatic genome editing efficiency or specificity—and no single acceptable off-target rate—that can be defined at this time, as this must be evaluated in light of the particular intended use and technique.

POTENTIAL USE OF GENOME EDITING FOR "ENHANCEMENT"

Other aspects of the public debate on genome editing concern its potential use for modifying physical traits and capacities beyond those considered typical of adequate health. For example, using somatic cell genome editing to improve musculature among patients with muscular dystrophy would be considered a restorative treatment, whereas using the same intervention for individuals with no known pathology and average capabilities to make them stronger might be considered an "enhancement." At this time, the potential benefits of such uses are unlikely to outweigh the risks. With additional research those risks will probably diminish, and it will become increasingly important to have public input on how to weigh the purported benefit of an enhancement against those risks.

There is some indication of public discomfort with using genome editing for enhancements, whether for fear of exacerbating social inequities or of creating social pressures that drive people to use technologies that simply are not necessary. Public discussion is important for exploring social impacts, both real and feared, as governance policy is developed. The committee concludes that somatic genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time.

GERMLINE EDITING FOR TREATMENT OR PREVENTION OF DISEASE OR DISABILITY

A third potential application of human genome editing involves alteration of germline cells to treat or prevent disease or disability. Germline genome editing has been conducted successfully in animals, but major technical challenges remain to be addressed 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 that are caused by mutations in single genes (see **https://www.omim.org**), and these genes could potentially be targeted in future germline editing applications. Editing germline cells could reduce the burden of inherited disease for a child and allow prospective parents who carry known disease-causing mutations to have genetically related offspring without the risk of passing mutations to their children.

Because germline genome editing would result in genetic changes being inherited by the next generation, it raises concerns about safety and unintended effects. It has also been argued that this degree of control in human reproduction crosses an ethically inviolable line. These discussions move the conversation about genome editing beyond individual-level risks and benefits and toward significantly more complex deliberations that touch on technical, social, and religious concerns about the appropriateness of this degree of intervention.

Given both the technical and societal concerns, the committee concludes there is a need for caution in any move toward germline editing, but that caution does not mean prohibition. It recommends that germline editing research trials might be permitted, but only after much more research to meet appropriate risk/benefit standards for authorizing clinical trials. Even then, germline editing should only be permitted for compelling reasons and under strict oversight. In the United States, authorities are currently unable to consider proposals for this research due to an ongoing prohibition on use of federal funds by FDA to review "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."

The committee defined a *set of criteria* under which heritable germline editing could be permitted if U.S. restrictions are allowed to expire, or if countries without legal prohibitions were to proceed with this line of research. The criteria includes:

- absence of reasonable alternatives;
- restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to a serious disease or condition;

RECAP OF MAJOR RECOMMENDATIONS

Basic Laboratory Research

- Use existing regulatory processes to oversee human genome editing laboratory research

Somatic Genome Editing

- Use existing regulatory processes for human gene therapy to oversee somatic human genome editing research and uses
- Limit clinical trials or therapies to treatment and prevention of disease or disability at this time
- Evaluate safety and efficacy in the context of risks and benefits of intended use
- Require broad public input prior to extending uses

Germline (Heritable) Genome Editing

- Permit clinical research trials only for compelling purposes of treating or preventing serious disease or disabilities, and only if there is a stringent oversight system able to limit uses to specified criteria
- Ongoing reassessment and public participation should precede any heritable germline editing

Enhancement

- Do not proceed at this time with human genome editing for purposes other than treatment or prevention of disease and disability
- Encourage public discussion and policy debate with respect to somatic human genome editing for uses other than treatment or prevention of disease and disability

- credible pre-clinical and/or clinical data on risks and potential health benefits;
- ongoing, rigorous oversight during clinical trials;
- comprehensive plans for long-term multigenerational follow-up; and
- continued reassessment of both health and societal benefits and risks, with wide-ranging, ongoing input from the public.

INCORPORATING PUBLIC ENGAGEMENT INTO REGULATORY OVERSIGHT

Public education and engagement are 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, the committee concludes that transparent and inclusive public policy debates should precede any consideration of whether to authorize clinical trials for indications that go beyond treatment or prevention of disease and disability (e.g. for enhancement). With respect to heritable germline editing, in addition to the strict criteria and stringent oversight discussed above, broad participation and input by the public, along with ongoing reassessment of both health and societal benefits and risks, should be a condition for moving clinical trials forward.

COMMITTEE ON HUMAN GENE EDITING: SCIENTIFIC, MEDICAL, AND ETHICAL CONSIDERATION

R. ALTA CHARO (*Co-Chair*), University of Wisconsin–Madison; **RICHARD O. HYNES** (*Co-Chair*), Howard Hughes Medical Institute and Massachusetts Institute of Technology; **DAVID W. BEIER,** Bay City Capital; **ELLEN WRIGHT CLAYTON**, Vanderbilt University; **BARRY S. COLLER**, Rockefeller University; **JOHN H. EVANS**, University of California, San Diego; **JUAN CARLOS IZPISUA BELMONTE**, Salk Institute for Biological Studies; **RUDOLF JAENISCH,** Massachusetts Institute of Technology; **JEFFREY KAHN**, Johns Hopkins University; **EPHRAT LEVY-LAHAD**, Shaare Zedek Medical Center and Hebrew University of Jerusalem; **ROBIN LOVELL-BADGE**, The Francis Crick Institute; **GARY MARCHANT**, Arizona State University; **JENNIFER MERCHANT**, Université de Paris II (Panthéon-Assas); **LUIGI NALDINI**, San Raffaele University and San Raffaele Telethon Institute for Gene Therapy; **DUANQING PEI**, Chinese Academy of Sciences; **MATTHEW PORTEUS**, Stanford School of Medicine; **JANET ROSSANT**, University of Toronto; **DIETRAM A. SCHEUFELE**, University of Wisconsin–Madison; **ISMAIL SERAGELDIN**, Bibliotheca Alexandrina; **SHARON TERRY**, Genetic Alliance; **JONATHAN WEISSMAN**, University of California, San Francisco; **KEITH R. YAMAMOTO**, University of California, San Francisco; **KATHERINE W. BOWMAN** (*Study Director*), **MONICA L. GONZALEZ** (*Associate Program Officer*), **JOANNA R. ROBERTS** (*Senior Program Assistant*), **ANDREW M. POPE** (*Director, Board on Health Sciences Policy*), **FRANCES E. SHARPLES** (Director, Board on Life Sciences)

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