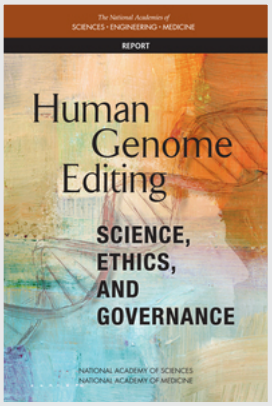

Human Genome Editing: Science, Ethics, and Governance (2017)

DETAILS

328 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-45288-5 | DOI 10.17226/24623

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SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2017. *Human Genome Editing: Science, Ethics, and Governance*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24623.

Summary[1]

enome editing[2] is a powerful new tool for making precise additions, deletions, and alterations to the genome—an organism's complete set of genetic material. The development of new approaches—involving the use of meganucleases; zinc finger nucleases (ZFNs); transcription activator-like effector nucleases (TALENs); and, most recently, the CRISPR/Cas9 system—has made editing of the genome much more precise, efficient, flexible, and less expensive relative to previous strategies. With these advances has come an explosion of interest in the possible applications of genome editing, both in conducting fundamental research and potentially in promoting human health through the treatment or prevention of disease and disability. The latter possibilities range from restoring normal function in diseased organs by editing somatic cells to preventing genetic diseases in future children and their descendants by editing the human germline.

As with other medical advances, each such application comes with its own set of benefits, risks, regulatory frameworks, ethical issues, and societal implications. Important questions raised with respect to genome editing include how to balance potential benefits against the risk of unintended

[1]This summary does not include references. Citations for the discussion presented in the summary appear in the subsequent report chapters.

[2]The term "genome editing" is used throughout this report to refer to the processes by which the genome sequence is changed by adding, replacing, or removing DNA base pairs. This term is used in lieu of "gene editing" because it is more accurate, as the editing could be targeted to sequences that are not part of genes themselves, such as areas that regulate gene expression.

harms; how to govern the use of these technologies; how to incorporate societal values into salient clinical and policy considerations; and how to respect the inevitable differences, rooted in national cultures, that will shape perspectives on whether and how to use these technologies.

Recognizing both the promise and concerns related to human genome editing, the National Academy of Sciences and the National Academy of Medicine convened the Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations to carry out the study that is documented in this report. While genome editing has potential applications in agriculture and nonhuman animals, this committee's task was focused on human applications. The charge to the committee included elements pertaining to the state of the science in genome editing, possible clinical applications of these technologies, potential risks and benefits, whether standards can be established for quantifying unintended effects, whether current regulatory frameworks provide adequate oversight, and what overarching principles should guide the regulation of genome editing in humans.

OVERVIEW OF GENOME-EDITING APPLICATIONS AND POLICY ISSUES

Genome-editing methods based on protein recognition of specific DNA sequences, such as those involving the use of meganucleases, ZFNs, and TALENs, are already being tested in several clinical trials for application in human gene therapy, and recent years have seen the development of a system based on RNA recognition of such DNA sequences. CRISPR (which stands for clustered regularly interspaced short palindromic repeats) refers to short, repeated segments of DNA originally discovered in bacteria. These segments provided the foundation for the development of a system that combines short RNA sequences paired with Cas9 (CRISPR associated protein 9, an RNA-directed nuclease), or with similar nucleases, and can readily be programmed to edit specific segments of DNA. The CRISPR/Cas9 genome-editing system offers several advantages over previous strategies for making changes to the genome and has been at the center of much discussion concerning how genome editing could be applied to promote human health. Like the use of meganucleases, ZFNs, and TALENs, CRISPR/Cas9 genome-editing technology exploits the ability to create double-stranded breaks in DNA and the cells' own DNA repair mechanisms to make precise changes to the genome. CRISPR/Cas9, however, can be engineered more easily and cheaply than these other methods to generate intended edits in the genome.

The fact that these new genome-editing technologies can be used to make precise changes in the genome at a high frequency and with considerable accuracy is driving intense interest in research to develop safe and

effective therapies that use these approaches and that offer options beyond simply replacing an entire gene. It is now possible to insert or delete single nucleotides, interrupt a gene or genetic element, make a single-stranded break in DNA, modify a nucleotide, or make epigenetic changes to gene expression. In the realm of biomedicine, genome editing could be used for three broad purposes: for basic research, for somatic interventions, and for germline interventions.

Basic research can focus on cellular, molecular, biochemical, genetic, or immunological mechanisms, including those that affect reproduction and the development and progression of disease, as well as responses to treatment. Such research can involve work on human cells or tissues, but unless it has the incidental effect of revealing information about an identifiable, living individual, it does not involve human subjects as defined by federal regulation in the United States. Most basic research on human cells uses somatic cells—nonreproductive cell types such as skin, liver, lung, and heart cells—although some basic research uses germline (i.e., reproductive) cells, including early-stage human embryos, eggs, sperm, and the cells that give rise to eggs and sperm. These latter cases entail ethical and regulatory considerations regarding how the cells are collected and the purposes for which they are used, even though the research involves no pregnancy and no transmission of changes to another generation.

Unlike basic research, clinical research involves interventions with human subjects. In the United States and most other countries with robust regulatory systems, proposed clinical applications must undergo a supervised research phase before becoming generally available to patients. Clinical applications of genome editing that target somatic cells affect only the patient, and are akin to existing efforts to use gene therapy for disease treatment and prevention; they do not affect offspring. By contrast, germline interventions would be aimed at altering a genome in a way that would affect not only the resulting child but potentially some of the child's descendants as well.

A number of the ethical, legal, and social questions surrounding gene therapy and human reproductive medicine provide a backdrop for consideration of key issues related to genome editing. When conducted carefully and with proper oversight, gene therapy research has enjoyed support from many stakeholder groups. But because such technologies as CRISPR/Cas9 have made genome editing so efficient and precise, they have opened up possible applications that have until now been viewed as largely theoretical. Germline editing to prevent genetically inherited disease is one example. Potential applications of editing for "enhancement"—for changes that go beyond mere restoration or protection of health—are another.

Because genome editing is only beginning to transition from basic research to clinical research applications, now is the time to evaluate the full

range of its possible uses in humans and to consider how to advance and govern these scientific developments. The speed at which the science is developing has generated considerable enthusiasm among scientists, industry, health-related advocacy organizations, and patient populations that perceive benefit from these advances. It is also raising concerns, such as those cited earlier, among policy makers and other interested parties to voice concerns about whether appropriate systems are in place to govern the technologies and whether societal values will be reflected in how genome editing is eventually applied in practice.

Public input and engagement are important elements of many scientific and medical advances. This is particularly true with respect to genome editing for potential applications that would be heritable—those involving germline cells—as well as those focused on goals other than disease treatment and prevention. Meaningful engagement with decision makers and stakeholders promotes transparency, confers legitimacy, and improves policy making. There are many ways to engage the public in these debates, ranging from public information campaigns to formal calls for public comment and incorporation of public opinion into policy.

APPLICATIONS OF HUMAN GENOME EDITING

Genome editing is already being widely used for basic science research in laboratories; is in the early stages of development of clinical applications that involve somatic (i.e., nonreproductive) cells; and in the future might be usable for clinical applications involving reproductive cells, which would produce heritable changes.

Basic Science Laboratory Research

Basic laboratory research involving genome editing of human cells and tissues is critical to advancing biomedical science. Genome-editing research using somatic cells can advance understanding of molecular processes that control disease development and progression, potentially facilitating the ability to develop better interventions for affected people. Laboratory research involving genome editing of germline cells can help in understanding human development and fertility, thereby supporting advances in such areas as regenerative medicine and fertility treatment.

The ethical issues associated with basic science research involving genome editing are the same as those that arise with any basic research involving human cells or tissues, and these issues are already addressed by extensive regulatory infrastructures. There are, of course, enduring debates about limitations of the current system, particularly with respect to how it addresses the use of gametes, embryos, and fetal tissue, but the regula-

tions are considered adequate for oversight of basic science research, as evidenced by their longevity. Special considerations may come into play for research involving human gametes and embryos in jurisdictions where such research is permitted; in those cases, the current regulations governing such work will apply to genome-editing research as well. Overall, then, basic laboratory research in human genome editing is already manageable under existing ethical norms and regulatory frameworks at the local, state, and federal levels.

Clinical Uses of Somatic Cell Editing for Treatment and Prevention of Disease and Disability

An example of the application of genome editing to alter somatic (nonreproductive) cells for purposes of treating or preventing disease is a recently authorized clinical trial involving patients whose advanced cancer has failed to respond to such conventional treatments as chemotherapy and radiation. In this study, genome editing is being used to program patients' immune cells to target the cancer.

Somatic cells are all those present in the tissues of the body except for sperm and egg cells and their precursors. This means that the effects of genome editing of somatic cells are limited to treated individuals and are not inherited by their offspring. The idea of making genetic changes to somatic cells—referred to as "gene therapy"—is not new, and genome editing for somatic applications would be similar. Gene therapy has been governed by ethical norms and subject to regulatory oversight for some time, and this experience offers guidance for establishing similar norms and oversight mechanisms for genome editing of somatic cells.

Somatic genome-editing therapies could be used in clinical practice in a number of ways. Some applications could involve removing relevant cells—such as blood or bone marrow cells—from a person's body, making specific genetic changes, and then returning the cells to that same individual. Because the edited cells would be outside the body (ex vivo), the success of the editing could be verified before the cells were replaced in the patient. Somatic genome editing also could be performed directly in the body (in vivo) by injecting a genome-editing tool into the bloodstream or target organ. Technical challenges remain, however, to the effective delivery of in vivo genome editing. Gene-editing tools introduced into the body might not find their target gene within the intended cell type efficiently. The result could be little or no health benefit to the patient, or even unintended harm, such as inadvertent effects on germline cells, for which screening would be necessary. Despite these challenges, however, clinical trials of in vivo editing strategies are already under way for hemophilia B and mucopolysaccharidosis I.

The primary scientific and technical, ethical, and regulatory issues associated with the use of somatic gene therapies to treat or prevent disease or disability concern only the individual. The scientific and technical issues of genome editing, such as the as-yet incompletely developed standards for measuring and evaluating off-target events, can be resolved through ongoing improvements in efficiency and accuracy, while the ethical and regulatory issues would be taken into account as part of existing regulatory frameworks that involve assessing the balance of anticipated risks and benefits to a patient.

Overall, the committee concluded that the ethical norms and regulatory regimes developed for human clinical research, gene transfer research, and existing somatic cell therapy are appropriate for the management of new somatic genome-editing applications aimed at treating or preventing disease and disability. However, off-target effects will vary with the platform technology, cell type, target gene, and other factors. As a result, no single standard for somatic genome-editing efficiency or specificity—and no single acceptable off-target rate—can be defined at this time. For this reason, and because, as noted above, somatic genome editing can be carried out in a number of different ways, regulators will need to consider the technical context of the genome-editing system as well as the proposed clinical application in weighing anticipated risks and benefits.

Germline Editing and Heritable Changes

Although editing of an individual's germline (reproductive) cells has been achieved in animals, there are major technical challenges to be addressed in developing this technology for safe and predictable use in humans. Nonetheless, the technology is of interest because thousands of inherited diseases are caused by mutations in single genes.[3] Thus, editing the germline cells of individuals who carry these mutations could allow them to have genetically related children without the risk of passing on these conditions. Germline genome editing is unlikely to be used often enough in the foreseeable future to have a significant effect on the prevalence of these diseases but could provide some families with their best or most acceptable option for averting disease transmission, either because existing technologies, such as prenatal or preimplantation genetic diagnosis, will not work in some cases or because the existing technologies involve discarding affected embryos or using selective abortion following prenatal diagnosis.

At the same time, however, germline editing is highly contentious precisely because the resulting genetic changes could be inherited by the next

[3]OMIM, https://www.omim.org (accessed January 5, 2017); Genetic Alliance, http://www.diseaseinfosearch.org (accessed January 5, 2017).

generation, and the technology therefore would cross a line many have viewed as ethically inviolable. The possibility of making heritable changes through the use of germline genome editing moves the conversation away from individual-level concerns and toward significantly more complex technical, social, and religious concerns regarding the appropriateness of this degree of intervention in nature and the potential effects of such changes on acceptance of children born with disabilities. Policy in this area will require a careful balancing of cultural norms, the physical and emotional well-being of children, parental autonomy, and the ability of regulatory systems to prevent inappropriate or abusive applications.

In light of the technical and social concerns involved, the committee concluded that heritable 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. It would be essential for this research to be approached with caution, and for it to proceed with broad public input.

In the United States, authorities currently are unable to consider proposals for this research because of an ongoing prohibition on the U.S. Food and Drug Administration's (FDA's) use of federal funds to review "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[4] In a number of other countries, germline genome-editing trials would be prohibited entirely. If U.S. restrictions on such trials were allowed to expire or if countries without legal prohibitions were to proceed with them, it would be essential to limit these trials only to the most compelling circumstances, to subject them to a comprehensive oversight framework that would protect the research subjects and their descendants, and to institute safeguards against inappropriate expansion into uses that are less compelling or well understood. In particular, clinical trials using heritable genome editing should be permitted only if done within a regulatory framework that includes the following criteria and structures:

- absence of reasonable alternatives;
- restriction to preventing a serious disease or condition;
- restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition;
- restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;

[4]Consolidated Appropriations Act of 2016, Public Law 114-113 (adopted December 18, 2015).

- availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures;
- ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;
- comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy;
- maximum transparency consistent with patient privacy;
- continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and
- reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

Even those who will support this recommendation are unlikely to arrive at it by the same reasoning. For those who find the benefits sufficiently compelling, the above criteria represent a commitment to promoting well-being within a framework of due care and responsible science. Those not completely persuaded that the benefits outweigh the social concerns may nonetheless conclude that these criteria, if properly implemented, are strict enough to prevent the harms they fear. It is important to note that such concepts as "reasonable alternatives" and "serious disease or condition" embedded in these criteria are necessarily vague. Different societies will interpret these concepts in the context of their diverse historical, cultural, and social characteristics, taking into account input from their publics and their relevant regulatory authorities. Likewise, physicians and patients will interpret them in light of the specifics of individual cases for which germline genome editing may be considered as a possible option. Starting points for defining some of these concepts exist, such as the definition of "serious disease or condition" used by the FDA.[5] Finally, those opposed to heritable editing may even conclude that, properly implemented, the above criteria are so strict that they would have the effect of preventing all clinical trials involving germline genome editing.

Use of Genome Editing for "Enhancement"

Although much of the current discussion around genome editing focuses on how these technologies can be used to treat or prevent disease and

[5]While not drafted with the above criteria in mind, the FDA definition of "serious disease or condition" is "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one" (21 CFR 312.300(b)(1)).

disability, some aspects of the public debate concern other purposes, such as the possibility of enhancing traits and capacities beyond levels considered typical of adequate health. In theory, genome editing for such enhancement purposes could involve both somatic and germline cells. Such uses of the technologies raise questions of fairness, social norms, personal autonomy, and the role of government.

To begin, it is necessary to define what is meant by "enhancement." Formulating this definition requires a careful examination of how various stakeholders conceptualize "normal." For example, using genome editing to lower the cholesterol level of someone with abnormally high cholesterol might be considered prevention of heart disease, but using it to lower cholesterol that is in the desirable range is less easily characterized, and would either intervention differ from the current use of statins? Likewise, using genome editing to improve musculature for patients with muscular dystrophy would be considered a restorative treatment, whereas doing so for individuals with no known pathology and average capabilities just to make them stronger but still within the "normal" range might be considered enhancement. And using the technology to increase someone's muscle strength to the extreme end of human capacity (or beyond) would almost certainly be considered enhancement.

Regardless of the specific definition, there is some indication of public discomfort with using genome editing for what is deemed to be enhancement, whether for fear of exacerbating social inequities or of creating social pressure for people to use technologies they would not otherwise choose. Precisely because of the difficulty of evaluating the benefit of an enhancement to an individual given the large role of subjective factors, public discussion is needed to inform the regulatory risk/benefit analyses that underlie decisions to permit research or approve marketing. Public discussion also is needed to explore social impacts, both real and anticipated, as governance policy for such applications is developed. The committee recommends that genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time, and that it is essential for these public discussions to precede any decisions about whether or how to pursue clinical trials of such applications.

Public Engagement

Public engagement is always an important part of regulation and oversight for new technologies. As noted above, for somatic genome editing, it is essential that transparent and inclusive public policy debates precede any consideration of whether to authorize clinical trials for indications that go beyond treatment or prevention of disease or disability (e.g., for enhancement). With respect to heritable germline editing, broad participation and

input by the public and ongoing reassessment of both health and societal benefits and risks are particularly critical conditions for approval of clinical trials.

At present, a number of mechanisms for public communication and consultation are built into the U.S. regulatory system, including some designed specifically for gene therapy, whose purview would include human genome editing. In some cases, regulatory rules and guidance documents are issued only after extensive public comment and agency response. Discussion is fostered by the various state and federal bioethics commissions, which typically bring together technical experts and social scientists in meetings that are open to the public. And the National Institutes of Health's Recombinant DNA Advisory Committee offers a venue for general public discussion of gene therapy, for review of specific protocols, and for transmission of advice to regulators. Other countries, such as France and the United Kingdom, have mechanisms that involve formal polling or hearings to ensure that diverse and informed viewpoints are heard.

PRINCIPLES TO GUIDE THE GOVERNANCE OF HUMAN GENOME EDITING

One of the charges to the committee was to identify principles that many countries might be able to use to govern human genome editing. The principles identified by the committee are detailed in Box S-1. The committee recommends that any nation considering governance of human genome editing consider incorporating these principles—and the responsibilities that flow therefrom—into its regulatory structures and processes.

RECOMMENDATIONS

In light of the considerations detailed above, the committee made a series of recommendations targeted to basic research and to clinical applications, both somatic and germline. A summary of the key messages in these recommendations is found in Box S-2.

BOX S-1
Principles for the Governance of Human Genome Editing

1. Promoting well-being: *The principle of promoting well-being supports providing benefit and preventing harm to those affected, often referred to in the bioethics literature as the principles of beneficence and nonmaleficence.*

Responsibilities that flow from adherence to this principle include (1) pursuing applications of human genome editing that promote the health and well-being of individuals, such as treating or preventing disease, while minimizing risk to individuals in early applications with a high degree of uncertainty; and (2) ensuring a reasonable balance of risk and benefit for any application of human genome editing.

2. Transparency: *The principle of transparency requires openness and sharing of information in ways that are accessible and understandable to stakeholders.*

Responsibilities that flow from adherence to this principle include (1) a commitment to disclosure of information to the fullest extent possible and in a timely manner, and (2) meaningful public input into the policy-making process related to human genome editing, as well as other novel and disruptive technologies.

3. Due care: *The principle of due care for patients enrolled in research studies or receiving clinical care requires proceeding carefully and deliberately, and only when supported by sufficient and robust evidence.*

Responsibilities that flow from adherence to this principle include proceeding cautiously and incrementally, under appropriate supervision and in ways that allow for frequent reassessment in light of future advances and cultural opinions.

4. Responsible science: *The principle of responsible science underpins adherence to the highest standards of research, from bench to bedside, in accordance with international and professional norms.*

Responsibilities that flow from adherence to this principle include a commitment to (1) high-quality experimental design and analysis, (2) appropriate review and evaluation of protocols and resulting data, (3) transparency, and (4) correction of false or misleading data or analysis.

5. Respect for persons: *The principle of respect for persons requires recognition of the personal dignity of all individuals, acknowledgment of the centrality of personal choice, and respect for individual decisions. All people have equal moral value, regardless of their genetic qualities.*

Responsibilities that flow from adherence to this principle include (1) a commitment to the equal value of all individuals, (2) respect for and promotion of individual decision making, (3) a commitment to preventing recurrence of the abusive

continued

BOX S-1 Continued

forms of eugenics practiced in the past, and (4) a commitment to destigmatizing disability.

6. Fairness: *The principle of fairness requires that like cases be treated alike, and that risks and benefits be equitably distributed (distributive justice).*

Responsibilities that flow from adherence to this principle include (1) equitable distribution of the burdens and benefits of research and (2) broad and equitable access to the benefits of resulting clinical applications of human genome editing.

7. Transnational cooperation: *The principle of transnational cooperation supports a commitment to collaborative approaches to research and governance while respecting different cultural contexts.*

Responsibilities that flow from adherence to this principle include (1) respect for differing national policies, (2) coordination of regulatory standards and procedures whenever possible, and (3) transnational collaboration and data sharing among different scientific communities and responsible regulatory authorities.

BOX S-2
Oversight and Use of Human Gene Editing:
Summary of Recommendations

Global Principles for Research and Clinical Use
Consider and apply the global principles in governance of human genome editing *(2.1)*

Promoting well-being
Transparency
Due care
Responsible science
Respect for persons
Fairness
Transnational cooperation

continued

BOX S-2 Continued

Basic Laboratory Research
Use existing regulatory processes to oversee human genome-editing laboratory research *(3.1)*

Somatic Genome Editing
Use existing regulatory processes for human gene therapy to oversee somatic human genome-editing research and uses *(4.1)*

Limit clinical trials or therapies to treatment and prevention of disease or disability at this time *(4.2)*

Evaluate safety and efficacy in the context of risks and benefits of intended use *(4.3)*

Require broad public input prior to extending uses *(4.4)*

Germline (Heritable) Genome Editing
Permit clinical research trials only for compelling purposes of treating or preventing serious disease or disability, and only if there is a stringent oversight system able to limit uses to specified criteria *(5.1)*

Enhancement
Do not proceed at this time with human genome editing for purposes other than treatment or prevention of disease and disability *(6.1)*

Encourage public discussion and policy debate with respect to somatic human genome editing for uses other than treatment or prevention of disease and disability *(6.2)*

Public Engagement
Public input should precede any clinical trials for an extension of human genome editing beyond disease treatment and prevention *(7.1)*

Ongoing reassessment and public participation should precede any clinical trials of heritable germline editing *(7.2)*

Incorporate public participation into the human genome editing policy process concerning "enhancement" *(7.3)*

When funding genome-editing research, consider including research on strategies to improve public engagement *(7.4)* and for long-term assessment of the ethical, legal, and social implications of human genome editing *(7.5)*