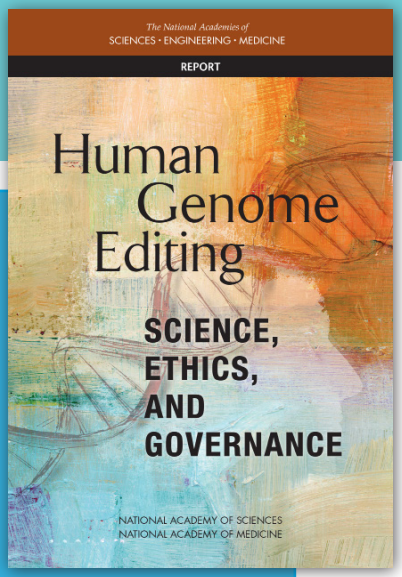
Human Genome Editing: Science, Ethics, and Governance

Highlights for Industry Stakeholders



Background

Advances in genome editing, especially the CRISPR/Cas9 genome editing system, have generated tremendous interest around the globe because of the ways these technologies can be used to develop new therapies aimed at improving human health. Once limited to the realm of basic science, these technologies are rapidly transitioning into clinical applications. Trials are already underway using genome editing to modify patients' immune system cells to target cancerous tumors, while other studies are using these methods to make cells more resistant to HIV. The progress in human genome editing offers opportunities for biotechnology companies and other entities in the private sector to develop therapies that capitalize on the power of these technologies.

As with other scientific advances that have direct applications to health and medicine, each new use of human genome editing carries a unique set of benefits, risks, regulatory issues, and societal implications. Important questions have been raised that have direct implications for companies that use, or may wish to develop, products that involve genomic editing technologies. Among the many questions that are of interest to the biotechnology sector and other industries are:

- What types of somatic and heritable (germline) editing studies can be done now and in the near future?
- What is the acceptable off-target rate in genome editing applications?
- What risk-benefit framework will be used to assess the appropriateness of human genome editing studies?
- Can genome editing studies explore "enhancements" – interventions to modify traits beyond those that are considered typical of adequate health?
- What role will public engagement play in ongoing development of human genome editing?

Industry stakeholders need answers to these questions in part because of their desire to make informed decisions about product development using genome editing technologies. To help develop guidance that industry and other stakeholders can use in their business and product planning efforts, the National Academy of Sciences and National Academy of Medicine convened the Committee on Human Gene Editing. This committee was charged with carrying out a study on the appropriate use and development of genome editing in people and the resulting findings and recommendations are presented in the report *Human Genome Editing: Science, Ethics, and Governance.*

The report concludes that genome editing holds promise for deepening understanding of biology and for ameliorating, treating, preventing, or maybe even eliminating a number of human diseases. However, it emphasizes that along with this promise comes the need for responsible and ethically sound frameworks for research and clinical applications. The report identifies seven principles that provide a foundation to guide human genome editing research and its clinical applications worldwide *(Box 1).* Based on these principles, the report makes a number of recommendations concerning appropriate use and oversight of human genome editing.

Box 1

Principles for the Governance of Human Genome Editing

1. **Promoting well-being:** providing benefit and preventing harm to those affected
2. **Transparency:** openness and sharing of information in ways that are accessible and understandable to stakeholders
3. **Due care:** proceeding carefully and deliberately, and only when supported by sufficient and robust evidence
4. **Responsible science:** adherence to the highest standards of research in accordance with international and professional norms
5. **Respect for persons:** recognition of the personal dignity of all individuals, acknowledgment of the centrality of personal choice, and respect for individual decisions
6. **Fairness:** risks and benefits should be equitably distributed
7. **Transnational cooperation:** a commitment to collaborative approaches to research and governance while respecting different cultural contexts

Basic Laboratory Research Using Genome Editing of Somatic and Germline Cells

Although most basic research on human tissues uses somatic cells, some work uses human germline cells. This work has resulted in important insights into areas as diverse as cancer, immunity, human fertility, miscarriage, fetal development, and regenerative medicine.

Basic research in human cells and tissues that uses genome editing is conducted under existing ethical norms and regulatory frameworks. In the United States, basic laboratory work involving recombinant DNA is regulated by federal law and overseen by local oversight bodies. Work involving human tissues that has the effect of identifying the tissue donor generally also is subject to regulations governing research with human subjects. Laboratory work involving human embryos currently is ineligible for federal funding, and is entirely prohibited in a small number of states.

The report concludes that the ethical issues associated with basic laboratory research involving human genome editing are the same as those for other basic research involving human cells or tissues, and that current regulations providing oversight for the latter research can also govern similar research for genome editing *(Box 2)*.

Special Considerations for Somatic Genome Editing

Making genetic changes to human somatic cells is not new in principle – gene therapy interventions are the basis of hundreds of early-stage, as well as a small number of late-stage, clinical trials aimed at treating inherited diseases. In general, the development of such therapies enjoys public support.

The report recommends that regulatory oversight of clinical trials of somatic genome editing should be the same as that

Box 2

Recommendation Concerning Basic Laboratory Research in Genome Editing

The report concludes that basic research involving both somatic and germline cells is essential to advancing science and should continue with existing regulatory structures. It does not propose new regulations for oversight of basic laboratory research using human genome editing.

used for other medical therapies. However, these assessments will need to consider the technical context of the genome editing system, as well as the proposed clinical application, so that anticipated risks and benefits can be appropriately weighed. Because off-target events vary with the platform technology, cell type, target genome sequence, and other factors, no single standard for the specificity of somatic genome editing can be defined at this time.

Although genome editing technology has expanded the potential applications of gene therapy, a distinction can be drawn between therapeutic applications of genome editing and using these techniques for "enhancements" aimed at modifying physical traits and capacities beyond those considered typical of adequate health. While genome editing techniques will continue to be improved, the report recommends that such techniques should only be used for treatment or prevention of disease and disability; use of genome editing for enhancements involves more risks than benefits and should not be permitted at this time *(Box 3).*

Heritable Genome Editing

Although advances in genome editing technology are driving improvements in the efficiency and accuracy of these techniques, off-target events are still a cause for concern. Applying these technologies to germline cells creates the potential that the impact of off-target events could be extended generations beyond the treated individual. In addition to concerns about safety and efficacy of heritable genome editing, the report notes that there is considerable apprehension about a broader set of ethical and cultural issues.

At present, clinical trials for heritable genome editing are not possible in the US due to budgetary restrictions, are illegal in a number of other countries, and are not yet technically feasible even where permitted. Even if current legal restrictions were removed, significantly more research is needed before any heritable intervention could be considered to meet the risk/benefit standard that is necessary to authorize clinical trials.

The report emphasizes that, although heritable genome editing trials must be approached with caution, this does not mean that they must be prohibited. If

Box 3
Recommendations Concerning Somatic Genome Editing

Existing regulatory infrastructure and processes for reviewing and evaluating somatic gene therapy to treat or prevent disease and disability should be used to evaluate somatic gene therapy that uses genome editing.

At this time, regulatory authorities should authorize clinical trials or approve cell therapies only for indications related to the treatment or prevention of disease or disability.

Oversight authorities should evaluate the safety and efficacy of proposed human somatic genome editing applications in the context of the risks and benefits of intended use, recognizing that off-target events may vary with the platform technology, cell type, target genomic location, and other factors.

Transparent and inclusive public policy debates should precede any consideration of whether to authorize clinical trials of somatic genome editing for indications that go beyond treatment or prevention of disease or disability.

Box 4
Criteria for Heritable Genome Editing

Clinical trials using heritable genome editing should be permitted only within a robust and effective regulatory framework that encompasses:

- The 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 that 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
- The availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures
- During any such trial, ongoing, rigorous oversight 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 on-going participation and input by the public
- Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition

technical challenges are overcome and potential benefits are reasonable relative to risks, clinical trials could be ethically permissible, but only if they meet a set of compelling criteria *(Box 4).* These criteria could be used as scaffolding for a future regulatory framework for heritable genome editing if current laws restricting heritable editing were eased. If it is not possible to satisfy these criteria, the report notes that trials involving heritable genome editing should not be permitted.

The Importance of Public Engagement

Rapid advances in genome editing have created increasing calls for broad public dialogue about these technologies and their applications. Public engagement can increase the public's perception of the legitimacy of regulatory or policy decisions about emerging technologies like genome editing. Many existing regulatory mechanisms, such as IRBs and the RAC, already involve public input, and the public has a means to provide input on funding priorities, regulations, and other aspects of basic research through electoral choices at the federal, state and local levels. However, weighing the technical and societal benefits and risks of applications of future uses of germline editing will require more formalized efforts to solicit public input and encourage public debate than are currently in place. Furthermore, the complex issues surrounding enhancement will require ongoing public debate to inform regulators and policymakers about the individual and societal values concerning risks and benefits before clinical trials for enhancement interventions should be authorized. The report recommends that extensive and inclusive public participation precede clinical trials for any extension of human genome editing beyond treatment or prevention of disease or disability, and that these discussions should also

precede consideration of any clinical trials of heritable genome editing. To this end, ongoing monitoring of public attitudes, information deficits, and emerging concerns will be essential. These public engagement efforts will allow agencies and other policy bodies to (1) communicate effectively by informing different audiences providing policy-relevant scientific information, and (2) identify areas requiring systematic efforts to create infrastructures for public engagement early in the process. Ongoing efforts to encourage public engagement need to be tied directly to the policy-making process.

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For more information, visit: www.national-academies.org/gene-editing

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