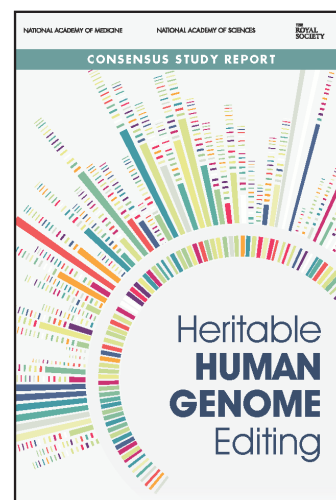


## Heritable Human Genome Editing

Rapidly advancing technical capabilities in genome editing, and the reported use of heritable human genome editing (HHGE) in 2018 leading to the birth of children whose DNA had been edited, led to renewed global calls for consideration of the scientific, societal, and governance issues associated with this technology. The possibility of heritable editing occurs when alterations to genomic DNA are made in gametes (eggs or sperm) or any cells that give rise to gametes, including the single cell zygote resulting from fertilization of an egg by a sperm cell, or cells of an early embryo. Changes made to the genetic material in such cells can be passed on to subsequent generations.



No country has yet decided that it would be appropriate to move forward clinically with HHGE, and clinical use of the technology is currently explicitly prohibited or not explicitly regulated in many countries. HHGE could represent an important option for prospective parents with a known risk of transmitting a genetic disease to have a genetically-related child without that disease and its associated morbidity and mortality. However, it will be essential to establish safe and effective methodologies that could form the necessary steps in a translational pathway for any clinical uses of HHGE. Assuming the existence of a safe and effective methodology, the decision to permit the clinical use of HHGE and, if so, for which specific applications, must ultimately rest with individual countries following informed societal debate of both ethical and scientific considerations.

This societal debate would include a range of issues and questions raised by HHGE, as well as how it might address important unmet needs within a country, informed by the views of patients and their families; ethical, moral, and religious views; potential long-term societal implications; and issues of cost and access. The societal considerations are the subject of ongoing national and international conversations, including current work by the World Health Organization's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which is deliberating on national and global governance.

The International Commission on the Clinical Use of Human Germline Genome Editing, which was convened by the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, and the U.K.'s Royal Society and includes members from 10 countries, was tasked with addressing the scientific considerations that would be needed to inform broader societal decision-making. This task involves considering technical, scientific, medical, and regulatory requirements, as well as those societal and ethical issues that are inextricably linked to these requirements, such as the significance of uncertainties related to outcomes, and potential benefits and harms to participants in clinical uses of HHGE.

This report does not make judgments about whether any clinical uses of a *safe and effective* HHGE methodology, if established by pre-clinical research, should at some point be permitted. The report instead seeks to determine whether the safety and efficacy of genome editing methodologies and associated assisted reproductive technologies are or could be sufficiently well developed to permit responsible clinical use of HHGE; identifies initial potential applications of HHGE for which a responsible clinical translational pathway can currently be defined; and delineates the necessary elements of such a translational pathway. It also elaborates national and international mechanisms necessary for appropriate *scientific* governance of HHGE, while recognizing that additional governance mechanisms may be needed to address societal considerations that lie beyond the Commission's charge. The boxes provide the full set of report recommendations; the Summary text provides the context for these.

## **Current State of Scientific Understanding**

To assess what would be needed for a responsible translational pathway toward HHGE requires evaluating the state of scientific understanding of the effects of making genetic changes and of the procedures necessary to perform and to characterize the results of genome editing in human germline cells and embryos.

### *The Connections between Genetic Changes and Health*

The ability to make changes to the human genome with predictable effects on health relies on detailed understanding of how DNA sequence variation contributes to the occurrence and risk of disease. Monogenic diseases are caused by mutation of one or both copies of a single gene. Examples include muscular dystrophy, beta-thalassemia, cystic fibrosis, and Tay-Sachs disease. With some notable exceptions, monogenic diseases are individually rare, but together the thousands of monogenic diseases impose significant morbidity and mortality on populations. Current knowledge of medical genetics suggests that the possibility of using HHGE to increase the ability of prospective parents to have biologically-related children who will not inherit certain monogenic diseases is a realistic one.

On the other hand, most common diseases are influenced by many common genetic variants that each have a small effect on disease risk. In addition, the risk of developing such diseases is often influenced by environmental factors such as diet and lifestyle choices, and by circumstances that are difficult to predict. Editing a gene variant associated with such a polygenic disease will typically have little effect on risk of the disease. Preventing the disease might be expected to require dozens or more different edits, some of which could produce adverse effects because of other biological roles the gene may play and other genetic networks with which it interacts. Scientific knowledge is not at a stage at which HHGE for polygenic diseases can be conducted effectively or safely. Similarly, there is insufficient knowledge to permit consideration of genome editing for other purposes, including nonmedical traits or genetic enhancement, because anticipated benefits in one domain might often be offset by unforeseen impact on risk of other diseases. Moreover, for these latter purposes the barrier to social acceptability would be particularly high.

### *Undertaking Genome Editing and Characterizing its Effects*

At present, the primary approach that could be used for undertaking HHGE would involve genome editing in zygotes. A zygote is the single, fertilized cell that results from the combination of parental gametes—the egg and sperm—and is the earliest stage in embryonic development. Although the pace of advances in developing genome editing methodologies

continues to be rapid, and ongoing research to overcome current scientific and technical challenges will continue to be valuable, significant knowledge gaps remain concerning how to control and characterize genome editing in human zygotes, as well as in the development of potential alternatives to zygote editing. Gaps that would need to be addressed include:

*Limitations in the Understanding of Genome Editing Technologies:* The outcomes of genome editing in human zygotes cannot be adequately controlled. No one has demonstrated that it is possible to reliably prevent (1) the formation of undesired products at the intended target site; (2) the generation of unintentional modifications at off-target sites, and (3) the production of mosaic embryos, in which intended or unintended modifications occur in only a subset of an embryo's cells; the effects of such mosaicism are difficult to predict. An appropriately cautious approach to any initial human uses would include stringent standards for preclinical evidence on each of these points.

*Limitations Associated with Characterizing the Effects of Genome Editing in Human Embryos:* Protocols suitable for preclinical validation of human editing would need to be developed to determine: (a) the efficiency of achieving desired on-target edits; (b) the frequency with which undesired edits are made; and (c) the frequency with which mosaic editing occurs.

**Recommendation 1:** No attempt to establish a pregnancy with a human embryo that has undergone genome editing should proceed unless and until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes in human embryos. These criteria have not yet been met and further research and review would be necessary to meet them.

### **Importance of Societal Decision-Making About Heritable Genome Editing**

This report focuses on whether a responsible translational pathway can be defined for some potential applications of HHGE. However, it is important to emphasize that the existence of a responsible clinical translational pathway does not mean that a clinical use of HHGE should proceed. Before any such clinical use, there must be widespread societal engagement and approval, and the establishment of national and international frameworks for responsible uses. This Commission highlights the importance of these societal considerations, while acknowledging that the appropriate mechanisms for addressing them lie beyond its charge.

**Recommendation 2:** Extensive societal dialogue should be undertaken before a country makes a decision on whether to permit clinical use of heritable human genome editing (HHGE). The clinical use of HHGE raises not only scientific and medical considerations, but also societal and ethical issues that were beyond the Commission's charge.

### **Categorizing Potential Uses of Heritable Genome Editing**

Prospective parents who know they are at risk of having a child affected by a monogenic disease already have various reproductive options. Among them is the use of in vitro fertilization (IVF) together with preimplantation genetic testing (PGT) to ensure that embryos judged suitable for transfer do not carry the disease genotype. In rare cases, every embryo a couple can produce will inherit the disease-causing genotype; for such prospective parents, HHGE could represent the only option to have a genetically-related child without the disease.

In all other groups of prospective parents, some of the embryos are expected not to carry the disease genotype, so PGT can enable them to have an unaffected child. However, a combination of genetic circumstances and reduced fertility can mean that PGT does not always result in the identification of an unaffected embryo for transfer. If HHGE could be performed safely, accurately, and without damaging embryos, it might be possible to increase the number of embryos without a disease genotype that could be used to establish a pregnancy, thereby decreasing the number of treatment cycles required. Whether a meaningful increase could be achieved is currently unclear and would need to be established empirically.

It is not possible to perform a generic benefit-harm analysis covering all possible applications of HHGE since any assessment will depend on the particular circumstances under consideration. One overarching principle that guided the Commission in identifying circumstances for which a responsible translational pathway could be defined was that the highest priority should be given to safety, with any initial uses offering the most favorable balance of potential harms and benefits.

**Recommendation 3:** It is not possible to define a responsible translational pathway applicable across all possible uses of heritable human genome editing (HHGE) because the uses, circumstances and considerations differ widely, as do the advances in fundamental knowledge that would be needed before different types of uses could be considered feasible.

Clinical use of HHGE should proceed incrementally. At all times, there should be clear thresholds on permitted uses, based on whether a responsible translational pathway can be and has been clearly defined for evaluating the safety and efficacy of the use, and whether a country has decided to permit the use.

**Recommendation 4:** Initial uses of heritable human genome editing (HHGE), should a country decide to permit them, should be limited to circumstances that meet all of the following criteria:

1. the use of HHGE is limited to serious monogenic diseases; the Commission defines a serious monogenic disease as one that causes severe morbidity or premature death;
2. the use of HHGE is limited to changing a pathogenic genetic variant known to be responsible for the serious monogenic disease to a sequence that is common in the relevant population and that is known not to be disease-causing;
3. no embryos without the disease-causing genotype will be subjected to the process of genome editing and transfer, to ensure that no individuals resulting from edited embryos were exposed to risks of HHGE without any potential benefit; and
4. the use of HHGE is limited to situations in which prospective parents: (i) have no option for having a genetically-related child that does not have the serious monogenic disease, because none of their embryos would be genetically unaffected in the absence of genome editing, or (ii) have extremely poor options, because the expected proportion of unaffected embryos would be unusually low, which the Commission defines as 25 percent or less, and have attempted at least one cycle of preimplantation genetic testing without success.

The report describes six categories of potential uses of HHGE, reflective of these four criteria:

(A) cases in which all of the prospective parents' children would inherit the disease-causing genotype for a serious monogenic disease (defined in this report as a monogenic disease that causes severe morbidity or premature death);

(B) cases in which some but not all of the prospective parents' children would inherit the pathogenic genotype for a serious monogenic disease;

- (C) cases involving other monogenic conditions with less serious impact;
- (D) cases involving polygenic diseases;
- (E) cases involving other applications of HHGE, including changes that would enhance or introduce new traits or attempt to eliminate certain diseases from the human population;
- (F) the special circumstance of monogenic conditions that cause infertility.

To meet all four criteria in Recommendation 4, and based on the available information, the Commission concluded that it is possible to define a responsible translational pathway for initial uses only in Category A and a very small set of circumstances in Category B. To meet the criteria in Category B, reliable methods would need to be developed to ensure that no individuals resulted from embryos that had been subjected to potential adverse consequences of genome editing without potential benefit. Such methods would depend either on identifying zygotes or embryos with the disease-causing genotype before performing HHGE or on excluding from transfer embryos that had needlessly undergone editing.

The Commission concluded that it was not currently possible to define a responsible translational pathway for initial clinical uses of HHGE for other circumstances.

### A Translational Pathway for Heritable Human Genome Editing

By a translational pathway for HHGE, the Commission means the steps that would be needed to enable a proposed clinical use to proceed from preclinical research to application in humans. The framework proposed by the Commission draws on experiences of developing a translational pathway for mitochondrial replacement techniques, other assisted reproductive technologies (ART), and from prior clinical experience in editing human somatic cells. If deemed acceptable by a country, HHGE would entail a form of ART used to generate and transfer to the uterus an embryo with an altered genome, resulting in the birth of an individual with this altered DNA.

A translational pathway for uses of HHGE would involve multiple stages (see Figure S-1). Preclinical evidence would need to be obtained from laboratory studies in cultured cells, editing in non-germline human tissues, studies in animal models, and laboratory research in early human embryos. These studies would need to establish that the desired edits can be made reliably, without additional alterations to the genome, and that the process does not alter normal development.

Should a country permit the clinical evaluation of HHGE and should relevant national regulatory

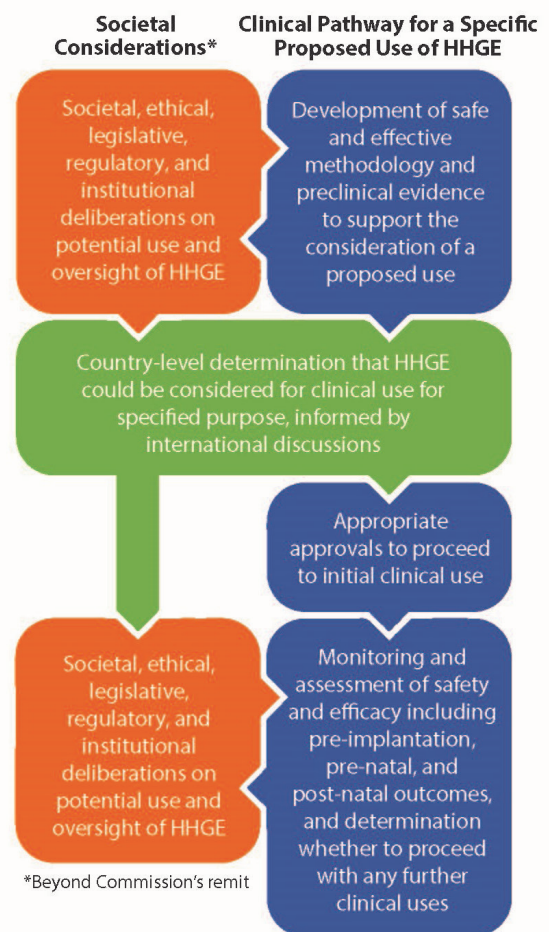


FIGURE S-1 The main elements of a clinical translational pathway for a proposed use of HHGE to enable parents to have a genetically-related child without a serious monogenic disease. The Commission's work focused on the clinical pathway elements on the right side.

authorities give authorization for initial human uses, an embryo with an edited genome would be created with the aim of transferring it to establish a pregnancy. Clinical testing would be undertaken to verify that the embryo had the desired genetic edit and no detectable additional changes that could cause potential harm. Other essential components of any pathway, such as plans for obtaining informed consent and for undertaking short-term and long-term follow up, would also be evaluated by the regulatory authority as part of the clinical approval process.

### **Scientific Validation and Standards for Any Proposed Use of Heritable Human Genome Editing**

The initial use of HHGE would represent a new technological intervention in the ART clinic, with only preclinical data with which to judge efficacy and safety. The goal of setting technical standards for HHGE would be to provide very high confidence that any transferred embryos would be correctly edited and that these embryos would have no additional potentially harmful changes introduced by the editing process. For any initial human uses, the standards would need to be set very high, because safety and efficacy could only be fully determined through human use. Preclinical and clinical research must be performed in accordance with the requirements of Recommendation 8.

**Recommendation 5:** Before any attempt to establish a pregnancy with an embryo that has undergone genome editing, preclinical evidence must demonstrate that heritable human genome editing (HHGE) can be performed with sufficiently high efficiency and precision to be clinically useful. For any initial uses of HHGE, preclinical evidence of safety and efficacy should be based on the study of a significant cohort of edited human embryos and should demonstrate that the process has the ability to generate and select, with high accuracy, suitable numbers of embryos that:

- have the intended edit(s) and no other modification at the target(s);
- lack additional variants introduced by the editing process at off-target sites—that is, the total number of new genomic variants should not differ significantly from that found in comparable unedited embryos;
- lack evidence of mosaicism introduced by the editing process;
- are of suitable clinical grade to establish a pregnancy;
- have aneuploidy rates no higher than expected based on standard assisted reproductive technology procedures.

**Recommendation 6:** Any proposal for initial clinical use of heritable human genome editing should meet the criteria for preclinical evidence set forth in Recommendation 5. A proposal for clinical use should also include plans to evaluate human embryos prior to transfer using:

- developmental milestones until the blastocyst stage comparable with standard in vitro fertilization practices; and
- a biopsy at the blastocyst stage that demonstrates
  - o the existence of the intended edit in all biopsied cells and no evidence of unintended edits at the target locus; and
  - o no evidence of additional variants introduced by the editing process at off-target sites.

If, after rigorous evaluation, a regulatory approval for embryo transfer is granted, monitoring during a resulting pregnancy and long-term follow up of resulting children and adults is vital.

## Future Developments Affecting Reproductive Options

Genome editing in precursor cells that can form eggs and sperm or editing of pluripotent stem cells followed by differentiation into functional gametes in vitro (in vitro–derived gametogenesis, IVG) represent potential alternatives to zygote genome editing for HHGE. The technologies to develop human gametes from cultured cells are still under development and are currently unavailable for clinical use. The same is true for the theoretical possibility of extracting human spermatogonial stem cells (SSCs), performing genome editing on them, and reimplanting them in the testes. Any future clinical use of IVG or reimplanted SSCs raises scientific and ethical issues that would require careful consideration, and the procedure would require approval as an assisted reproductive technology before it could be used for HHGE.

Genome editing using IVG could address many technical challenges associated with genome editing in zygotes. Methods for characterizing on- and off-target editing are well documented in cultured cells, and only correctly edited cells could be selected and differentiated into functional gametes. Mosaicism would not be an issue when a single sperm derived from an edited induced pluripotent stem cell (iPSC) is used to fertilize a single egg. However, iPSCs and gametes produced from them are likely to undergo adaptation to and expansion in cell culture, which may introduce other types of genetic and epigenetic changes that would need to be carefully assessed.

**Recommendation 7:** Research should continue into the development of methods to produce functional human gametes from cultured stem cells. The ability to generate large numbers of such stem cell–derived gametes would provide a further option for prospective parents to avoid the inheritance of disease through the efficient production, testing, and selection of embryos without the disease-causing genotype. However, the use of such in vitro–derived gametes in reproductive medicine raises distinct medical, ethical, and societal issues that must be carefully evaluated, and such gametes without genome editing would need to be approved for use in assisted reproductive technology before they could be considered for clinical use of heritable human genome editing.

## Essential Elements of Oversight Systems for Heritable Human Genome Editing

From a scientific perspective on safety and efficacy, considerations for any clinical use of HHGE should proceed incrementally. The initial focus would be on potential uses for which available knowledge has established an evidence base that, along with adherence to clinical and ethical norms, makes it possible to define a responsible translational pathway. However, any responsible translational pathway toward potential clinical uses of HHGE requires more than the technical and clinical pathway components. A translational pathway also requires having a comprehensive system for governing any continued development and use of HHGE. It will be important for national and international discussions to establish these governance processes prior to any clinical use under any envisioned circumstance. The work of the World Health Organization’s Expert Advisory Committee on Human Genome Editing will be important in this respect.

Governance of HHGE requires a multilayered system of responsibilities. Each country that considers the development of HHGE will end up drawing on the regulatory infrastructure and oversight authorities available under its laws and regulations. But all countries in which HHGE is being researched or conducted would need to have mechanisms in place to oversee translational progress toward potential clinical use of HHGE, to prevent unapproved uses, and to sanction

any misconduct. It is recognized that not all countries necessarily have the scientific expertise and regulatory and societal engagement mechanisms to meet the requirements listed below. Nonetheless, if a country is not able to meet all these conditions, no clinical use of HHGE should occur in that country.

**Recommendation 8:** Any country in which the clinical use of heritable human genome editing (HHGE) is being considered should have mechanisms and competent regulatory bodies to ensure that all of the following conditions are met:

- individuals conducting HHGE-related activities, and their oversight bodies, adhere to established principles of human rights, bioethics, and global governance;
- the clinical pathway for HHGE incorporates best practices from related technologies such as mitochondrial replacement techniques, preimplantation genetic testing, and somatic genome editing;
- decision-making is informed by findings from independent international assessments of progress in scientific research and the safety and efficacy of HHGE, which indicate that the technologies are advanced to a point that they could be considered for clinical use;
- prospective review of the science and ethics of any application to use HHGE is diligently performed by an appropriate body or process, with decisions made on a case-by-case basis;
- notice of proposed applications of HHGE being considered is provided by an appropriate body;
- details of approved applications (including genetic condition, laboratory procedures, laboratory or clinic where this will be done, and national bodies providing oversight) are made publicly accessible, while protecting family identities;
- detailed procedures and outcomes are published in peer-reviewed journals to provide dissemination of knowledge that will advance the field;
- the norms of responsible scientific conduct by individual investigators and laboratories are enforced;
- researchers and clinicians show leadership by organizing and participating in open international discussions on the coordination and sharing of results of relevant scientific, clinical, ethical, and societal developments impacting the assessment of HHGE's safety, efficacy, long-term monitoring, and societal acceptability;
- practice guidelines, standards, and policies for clinical uses of HHGE are created and adopted prior to offering clinical use of HHGE; and
- reports of deviation from established guidelines are received and reviewed, and sanctions are imposed where appropriate.

National decision-making should be informed by transparent international discussions before any country's regulatory authorities make major threshold decisions on uses of HHGE. The scientific assessment of whether the suite of technologies on which HHGE would depend have met clear scientific and safety thresholds to be considered for clinical use in a particular set of circumstances will be an essential contribution to both national and international discussions. There is, therefore, a need to regularly review the latest scientific evidence and to evaluate its potential impact on the feasibility of HHGE. The necessary functions of such scientific review include:

- assessing or making recommendations on further research developments that would be required to reach technical or translational milestones as research on HHGE progresses;
- providing information to national regulatory authorities or their equivalents to inform their own assessment and oversight efforts;
- facilitating coordination or standardization of study designs to promote the ability to compare



and pool data across studies and trans-nationally;

- advising on specific measures to be used as part of the long-term follow up of any children born following HHGE; and
- reviewing data on clinical outcomes from any regulated uses of HHGE and advising on the potential risks and benefits of possible further applications.

Although there are existing international scientific review bodies that fulfill some of these functions, the Commission does not believe there is an existing mechanism that adequately fulfills all of the functions. The Commission therefore recommends the establishment of a new body, which it has called the International Scientific Advisory Panel.

**Recommendation 9:** An International Scientific Advisory Panel (ISAP) should be established with clear roles and responsibilities before any clinical use of heritable human genome editing (HHGE). The ISAP should have a diverse, multidisciplinary membership and should include independent experts who can assess scientific evidence of safety and efficacy of both genome editing and associated assisted reproductive technologies. The ISAP should:

- provide regular updates on advances in, and the evaluation of, the technologies that HHGE would depend on and recommend further research developments that would be required to reach technical or translational milestones;
- assess whether preclinical requirements have been met for any circumstances in which HHGE may be considered for clinical use;
- review data on clinical outcomes from any regulated uses of HHGE and advise on the scientific and clinical risks and potential benefits of possible further applications; and
- provide input and advice on any responsible translational pathway to the international body described in Recommendation 10, as well as at the request of national regulators.

Before crossing any threshold to a new class of use of HHGE, it will be important for the global community to assess not only progress in scientific research, but also what additional ethical and societal concerns the circumstances of particular uses could raise, as well as any results, successes, or concerns that had been observed from any human uses of HHGE that had been conducted thus far. New classes of use may or may not precisely align with the six Categories defined above. A credible process would need to assess whether it is feasible to envision new translational pathways and what they should entail, and such a body would need not only experts in science, medicine, and ethics but also representatives from the many additional stakeholder communities that could be affected by future uses of HHGE.

**Recommendation 10:** In order to proceed with applications of heritable human genome editing (HHGE) that go beyond the translational pathway defined for initial classes of use of HHGE, an international body with appropriate standing and diverse expertise and experience should evaluate and make recommendations concerning any proposed new class of use. This international body should:

- clearly define each proposed new class of use and its limitations;
- enable and convene ongoing transparent discussions on the societal issues surrounding the new class of use;
- make recommendations concerning whether it could be appropriate to cross the threshold of permitting the new class of use; and
- provide a responsible translational pathway for the new class of use.

Finally, one other required component of any oversight system is a mechanism for raising concerns about research or clinical use of HHGE, and particularly one allowing a researcher or clinician to bring forward concerns arising from work conducted either in their own or in another country.

**Recommendation 11:** An international mechanism should be established by which concerns about research or conduct of heritable human genome editing that deviates from established guidelines or recommended standards can be received, transmitted to relevant national authorities, and publicly disclosed.

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