INTERNATIONAL COMMISSION ON THE CLINICAL USE OF HUMAN GERMLINE GENOME EDITING

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NATIONAL ACADEMY OF MEDICINE AND NATIONAL ACADEMY OF SCIENCES

THE ROYAL SOCIETY

Why, what, how?

- International Summits on Human Genome Editing

  2015, Washington D.C.

  2018, Hong Kong

- Calls for a translational pathway for heritable human genome editing (HHGE) in 2015

- Announcement in 2018 that attempts to create genome edited babies had already been made

Why, what, how?

The National Academies of SCIENCES ENGINEERING MEDICINE

THE ROYAL SOCIETY

- An international commission was convened by the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, and the U.K.'s Royal Society
- 18 Commissioners from ten countries with expertise in genome editing and assisted reproduction technologies, genetics, regulation, social science and law
- Every continent except Antarctica represented between Commissioners, speakers and reviewers

Commission and task

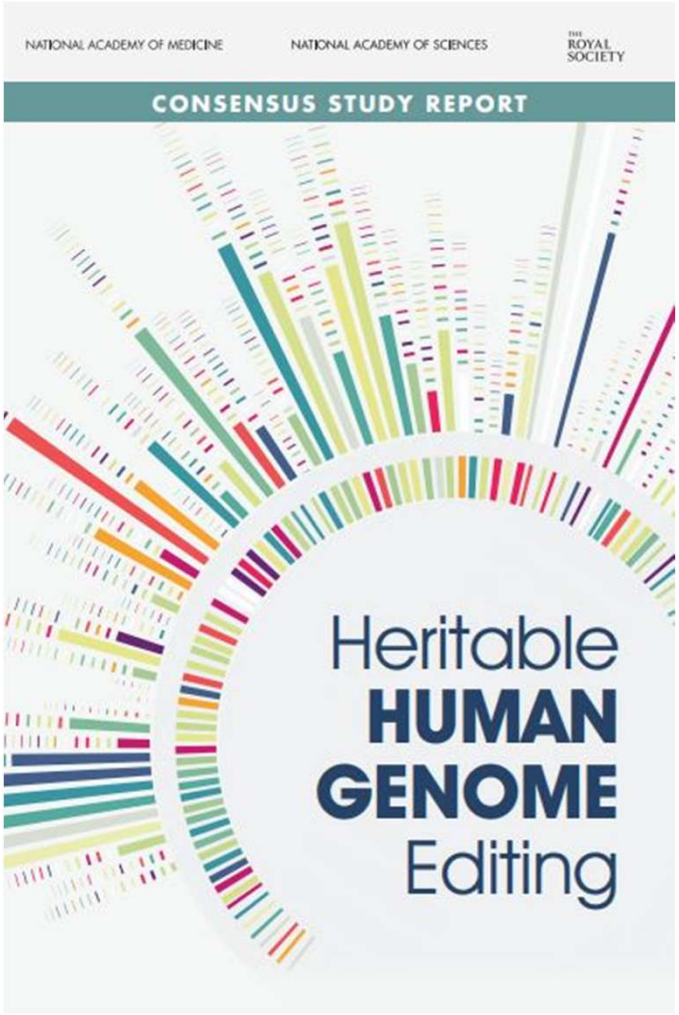
#HHGECommission

Commission's task

- Develop a framework for a responsible clinical translational pathway for initial uses of heritable human genome editing, if a society decides to permit them
- Consider technical, scientific, medical, and regulatory requirements, as well as those societal and ethical issues that are inextricably linked to these
- Not charged with addressing broader societal and ethical issues on HHGE
- WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing

Why, what, how?

- Three physical meetings and many zoom meetings during 2019 and 2020
- Two evidence-gathering workshops and a public call for evidence



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Report September 2020

Scientific background

11 recommendations

- Report evaluates current state of technologies on which any clinical use of HHGE would depend, the science on genetic basis of disease, and alternatives for assisted reproduction

- **Criteria for safe and effective HHGE have not yet been met.** Neither the editing technologies nor the technologies for sequencing embryonic DNA to check on-target and off-target effects are reliable enough for clinical use

Key messages

Recommendation 1-4

- No clinical use of HHGE should be considered until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes in human embryos. Further research is necessary

- Before any country decides to approve the use of HHGE, there should be national and international mechanisms to ensure that the preclinical requirements have been met for initial responsible use

- Any clinical use of HHGE should proceed cautiously and incrementally, with initial uses restricted to a limited set of circumstances.

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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.

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.

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.

Key messages
Recommendation 1-4

- Possible applications of HHGE categorized based on:
  - phenotype that editing is intended to influence
  - causal relationship between genotype and phenotype
  - alternative options available to prospective parents

- Six categories of possible applications
  - Category A – serious monogenic (single gene) diseases in which all children would inherit the disease
  - Category B – serious monogenic diseases in which some children would inherit the disease
  - Category C – monogenic conditions with less serious impacts
  - Category D – polygenic diseases
  - Category E – applications not related to heritable disease
  - Category F – monogenic conditions that cause infertility

Key messages
Recommendation 1-4

Analysis of the potential harms, benefits and uncertainties in the science, led to recommendation that any initial use of HHGE be restricted to circumstances that meet four criteria:

- Serious monogenic disease
- Common variant known not to cause disease
- No unaffected embryos subject to editing and transfer
- No or very poor options for having a genetically–related child without the disease

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.

Translational pathway for initial use

Recommendation 5-7

- Preclinical research in cell and animal models to develop and validate the editing methodology
- Sufficient preclinical evidence from human embryos to demonstrate
  - Reliably accurate on-target changes
  - No off-target changes introduced by the editing reagents
  - No mosaicism caused by the editing reagents
- Clinical evaluation of an embryo to be used in a pregnancy to verify
  - intended edit and no unintended changes in one or a few biopsied cells
  - Comparable developmental milestones as an unedited embryo
- Protocols for seeking informed consent and conducting long-term follow-up

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; and
- 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
    - the existence of the intended edit in all biopsied cells and no evidence of unintended edits at the target locus; and
    - 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.

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.

Governance arrangements for HHGE

National

Recommendation 8

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- National sovereignty in decision making
- Any country considering HHGE should have mechanisms and competent regulatory bodies to ensure that a number of conditions are met. If a country is not able to meet all of these conditions, no clinical use of HHGE should occur in that country. Conditions include:
  - National decision making should be informed by international consideration of the technologies
  - Case by case evaluation
  - Transparency

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.

Governance arrangements for HHGE

International
Recommendation 9-11

Three functions for international oversight of HHGE:

1. Ongoing evaluation of the science and technology on which HHGE would depend
   - International Scientific Advisory Panel (ISAP) to assess progress & research developments required to reach technical or translational milestones
   - assess whether preclinical requirements have been met for any circumstances of clinical use
   - advise on scientific and clinical risks and potential benefits
2. Debate whether it could be appropriate to cross HHGE thresholds to new class of uses, including ethical and societal concerns raised
   - international body to convene debates about crossing any HHGE thresholds. Diverse membership, beyond scientific and clinical expertise
   - role in defining each proposed new class of use and its limitations
   - recommend whether it could be appropriate to cross the threshold of permitting a new class of use
3. A mechanism for raising concerns about research or conduct of HHGE

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.

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.

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.

Taking the Commission's work forward

- Public briefings at conferences and Academy events
- Report being considered by World Health Organisation's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing
- WHO Report July 2021
- Revisiting the conclusions and recommendations at the Third International Summit on Human Genome Editing March 2022

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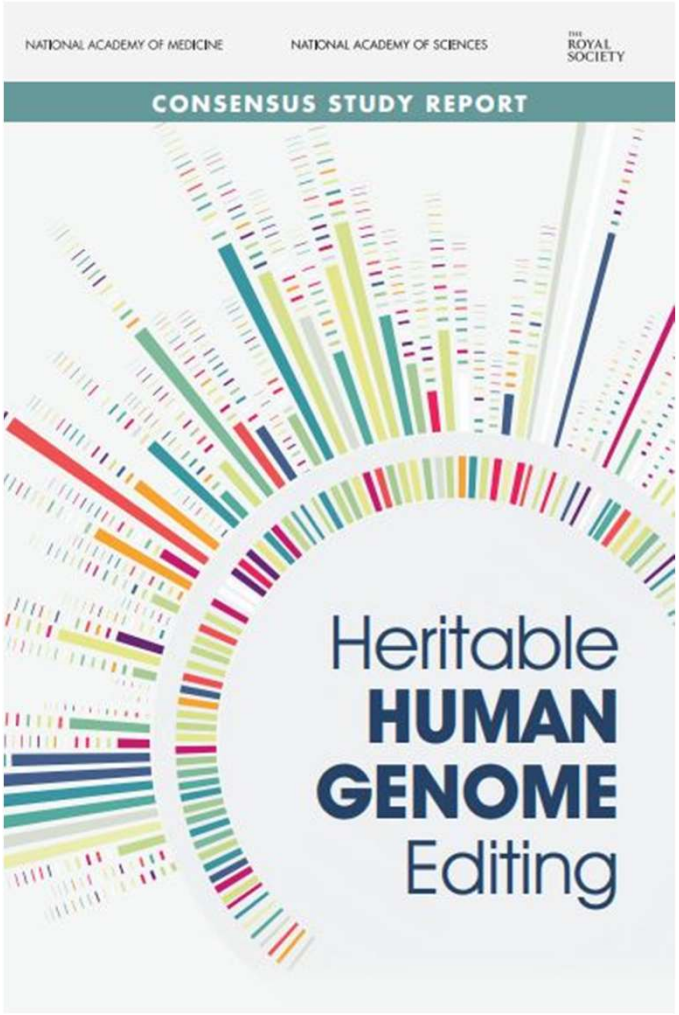

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