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Genome editing: scientific opportunities, public interests and policy options in the European Union

Human genome editing

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The Hinxton Group

An International Consortium on Stem Cells, Ethics & Law

Statement on Genome Editing Technologies and Human Germline Genetic Modification

4 September 2015

INTERNATIONAL SUMMIT ON HUMAN GENE EDITING

A GLOBAL DISCUSSION

December 1-3, 2015 Washington, D.C.

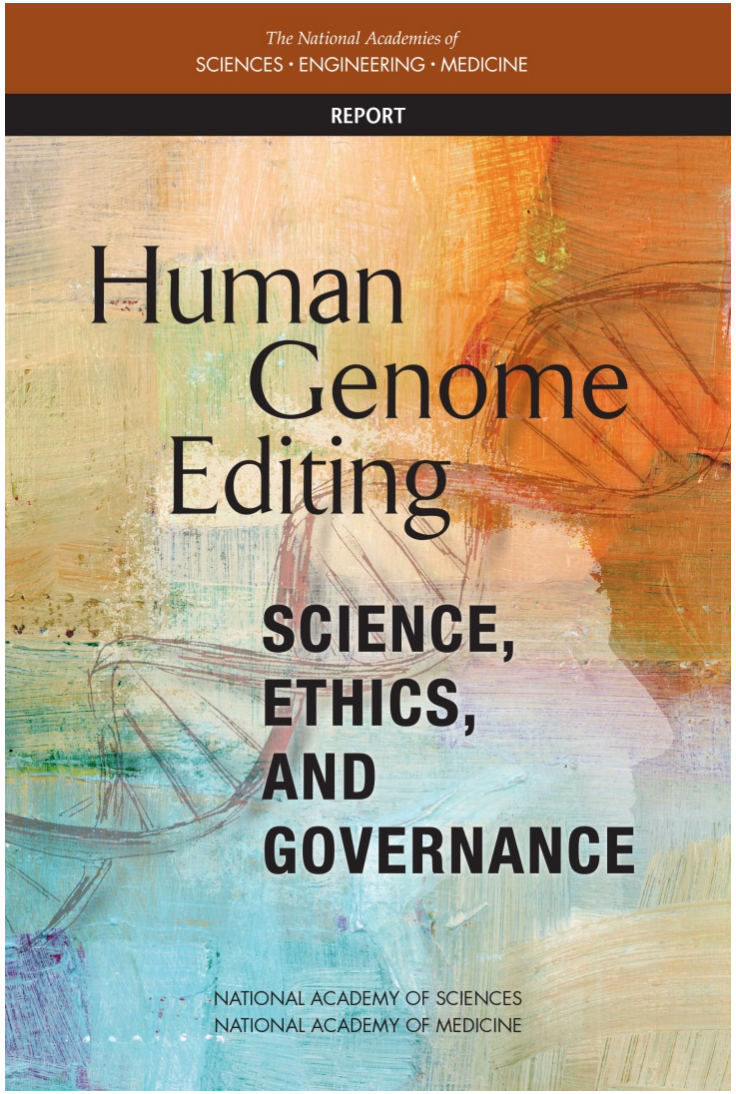
04 December 2016

FEAM

Human Genome Editing in the EU

Report of a workshop held on 28th April 2016 at the French Academy of Medicine

28 April 2016



National Academies of Sciences and National Academy of Medicine Report, Released on 14 February 2017

Why so many debates and reports now, about the possibility of altering the human genome ?

This is far from a new topic :

The concerns about “designer babies” and “eugenics” have arisen with each new method developed over the last 40 years, including:

- Recombinant DNA
- Transgenic animals made by pronuclear injection
- In vitro fertilisation (IVF)
- Gene targeting via homologous recombination in Embryonic Stem cells (ES cells)
- Preimplantation Genetic Diagnosis
- Cloning mammals, Human ES cells, iPS cells, etc.

But it until now it has always been possible to say that the methods are too inefficient and/or unsafe to apply to humans.

With genome editing, and particularly CRISPR/Cas9, the same arguments may no longer apply.

Conclusion of both the NAS/RS/CAS Summit meeting in Washington DC December 2015 and the EASAC Report:

"It would be irresponsible to proceed with any clinical use of germline editing unless and until:

(i) the relevant safety and efficacy issues have been resolved … and

(ii) there is broad societal consensus about the appropriateness of the proposed application."

The conclusions of the NAS Study Committee Report in 2017 were more permissive.

- It was recognised that the remaining safety and efficacy issues would be resolved, possibly in the near future.
- And that while public views were still critical, there seemed to be a growing consensus, at least among certain “publics”, that heritable germline genome editing might be acceptable - within limits.

But it was recognised that public engagement around the issues was still a challenge – notably how to do it well and in a meaningful way ?

And that the establishment of appropriate and robust regulations and oversight were critical – indeed it should not proceed in a jurisdiction until these were in place.

Overarching Principles for Governance of Human Genome Editing

- Promoting well-being
- Due Care
- Transparency
- Responsible Science
- Respect for Persons
- Fairness
- Transnational Cooperation

Any nation considering governance of human genome editing can incorporate these principles—and the responsibilities that flow from them—into its regulatory structures and processes.

Three major applications of genome editing with human cells

RESEARCH

- **Basic research (purely laboratory) work on cells and tissues**

CLINICAL

- **Somatic (non-heritable) interventions in patients to treat or prevent disease**

- **Germline (heritable) interventions to treat or prevent disease**

Basic Research

- **Basic research uses:**
  - **somatic cells (e.g., blood, liver, heart, brain cells)**
  - **germline cells (e.g., eggs, sperm, early-stage embryos)**
  - **pluripotent stem cells (e.g., ES and iPS cells)**
- **Important to advance understanding of:**
  - **gene functions and regulation,**
  - **DNA-repair mechanisms,**
  - **Cell biology, stem cells and immunity,**
  - **Human fertility, reproduction and fetal development,**
  - **Links between genes and disease,**
  - **Progression treatment of diseases with a strong genetic component**

Experiments in vitro to understand human biology

These are already common, with a variety of human cell culture systems in vitro, for example:

- Organ-specific stem cells, e.g. neural stem cells, gut stem cells.
- Embryonic Stem (ES) cells and induced pluripotent stem (iPS) cells, which can be differentiated in vitro to:
  - Specific cell types: neurons, primordial germ cells, etc.
  - Complex tissues: cortical brain structures, optic cups, kidney-like structures, etc.

- The role of specific genes and the effect of naturally occurring mutations can be studied in the context of specific genetic backgrounds.
- For example, genome editing can be used to copy a natural mutation in ES cells or iPS cells or to correct a mutant gene in patient-specific iPS cells.
- Such cells can also be used for screening drugs.

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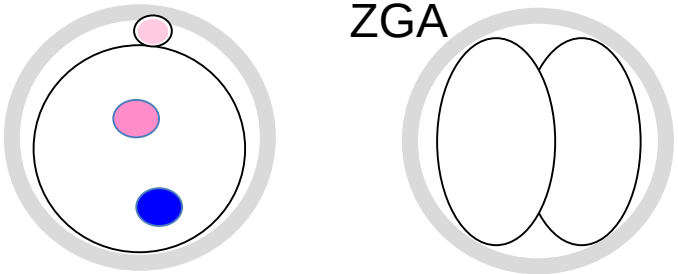
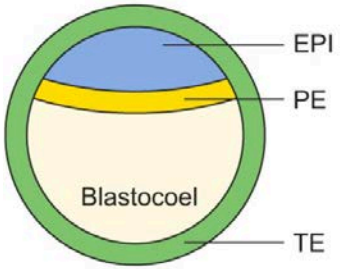
Why not use the techniques to study preimplantation embryos and other germline cells ……

Comparison of blastocyst and early post-implantation development between mouse and human.

MOUSE





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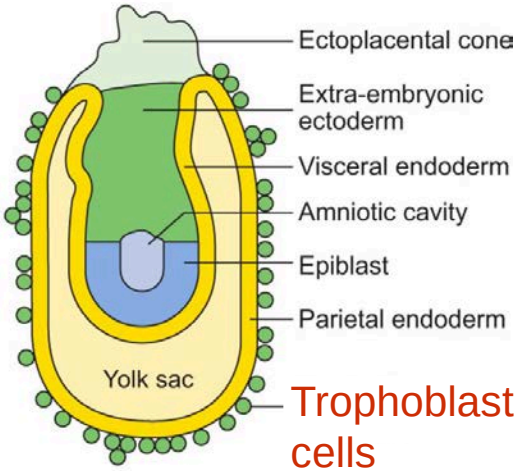

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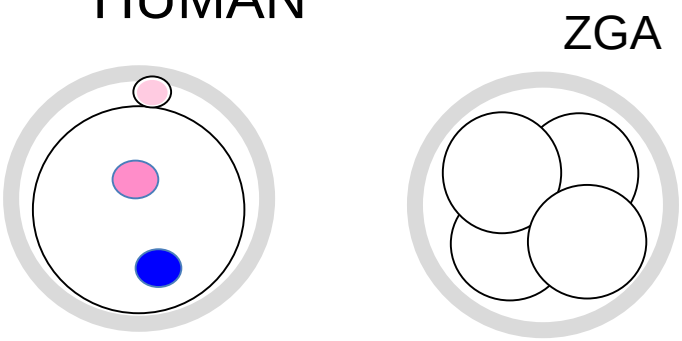
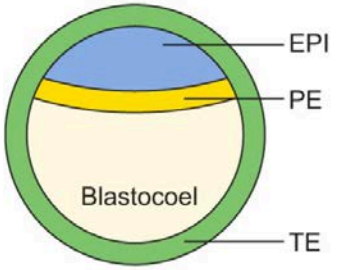
HUMAN





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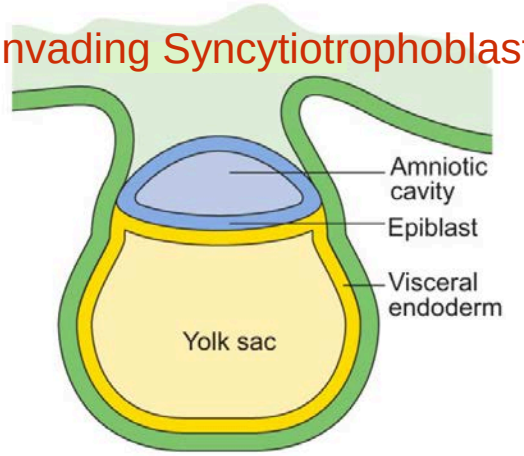

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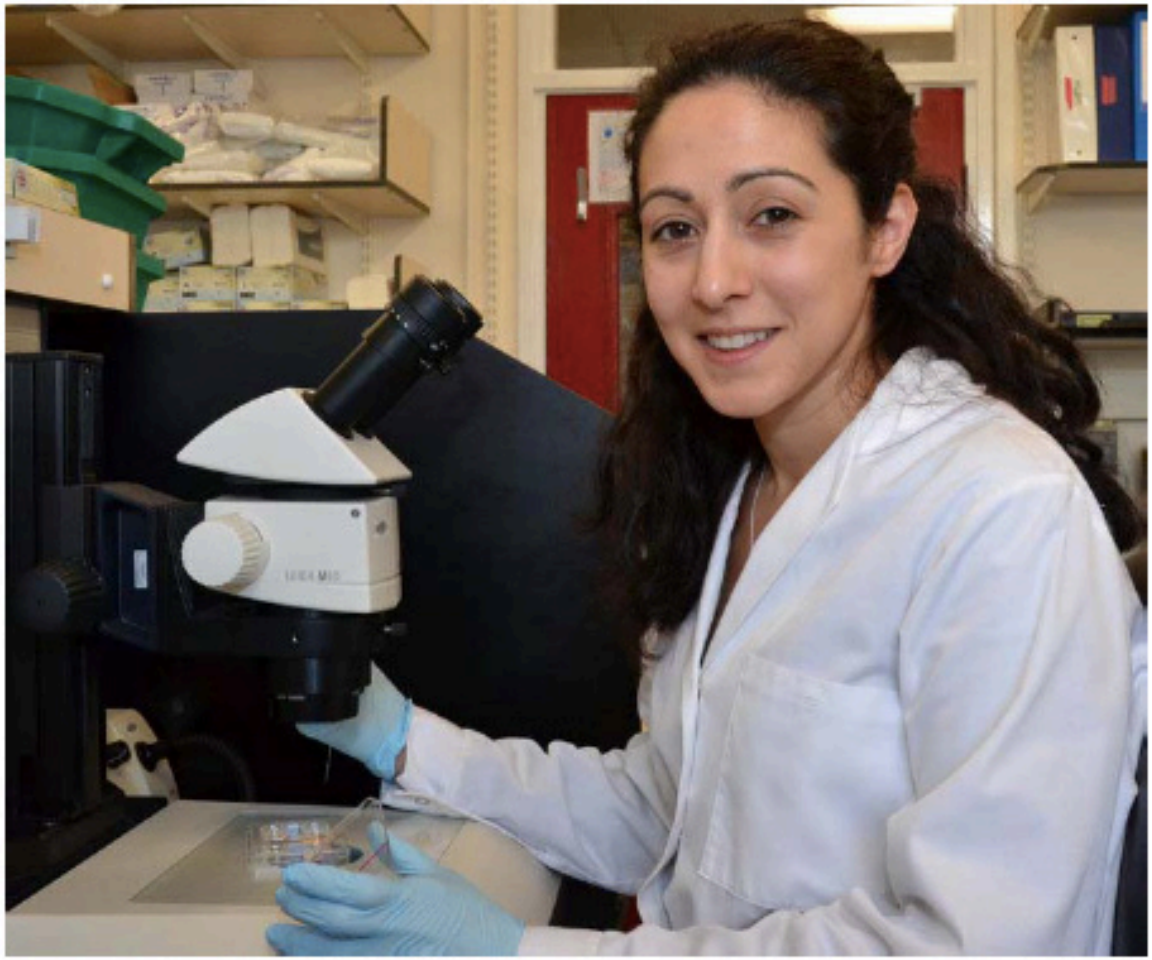
RNA expression studies show many differences in gene activity between mouse and human embryos

Adapted from Rossant (2015), Development 142:9-12

Research	Possible applications
How cell types are specified in the early human embryo, and the nature and importance of the genes involved.	Improved techniques for culturing embryos following IVF, better implantation rates, fewer miscarriages.
Understanding the biology and genetics of stem-cell lines representing the cell lineages thought to exist in the early human embryo – including non-embryonic cells such pregenitors of the placenta and yolk sac.	Improved ability to establish stem-cell lines for research, screens drugs for embryo/placenta toxicity or beneficial effects to prevent miscarriage. Reduction in embryos needed for research.
The role of specific genes in human germ-cell development, including the differentiation of sperm and eggs.	Fertility enhancement and the development of novel contraceptives.
Genome editing techniques	Improved efficiency and versatility of genome editing in early embryos and germline cells. Reduction in numbers of embryos required in experiments.



HFEA approves licence application to use gene editing in research

01 February 2016

Our Licence Committee has approved an application from Dr Kathy Niakan of the Francis Crick Institute to renew her laboratory's research licence to include gene editing of embryos.

The committee has added a condition to the licence that no research using gene editing may take place until the research has received research ethics approval.

As with all embryos used in research, it is illegal to transfer them to a woman for treatment.

The minutes and inspection report are available here.

Regulation of basic research in Europe:

This mostly concerns issues of safety, consent, and data protection, which are generally well covered.

However, the contentious issues involve research with early human embryos, which may be:

- Left over after IVF treatments and donated by couples
- Created for research

But these issues are not unique to research involving genome editing, which is after all just another method (albeit a very powerful and efficient one) to ask questions about the biology of early development, to improve IVF, reduce miscarriages, etc.

Somatic Therapy

- **Genome editing is a relatively new tool for gene therapy**
- **Approaches for somatic interventions:**
  - **outside the body (*ex vivo*) by removing cells, editing them and reinserting them**
    - **Ex: editing blood cells for treatments of cancer (immunotherapy) or HIV**
    - **Ex: editing blood cells for sickle cell disease, thalassemias**
  - **directly in the body (*in vivo)* by injection, which carries more technical challenges at this time**
    - **Ex: editing liver cells for hemophilia**
    - **Ex: editing muscle cells for muscular dystrophy**

N.B. Generally done on children/adults but might also become useful for in utero fetal therapy, e.g., using edited stem or progenitor cells

Somatic Therapy - Regulation

- **Institutional Biosafety Committees**
- **Institutional Review Boards**
  - **Protection of subjects in clinical trials; informed consent**
- **Recombinant DNA Advisory Committee**
  - **Advice and some protocol review; venue for public discussion**

USA: FDA

Europe: Multiple agencies

Control over initiating clinical trials
Control over approval for clinical use
Long term follow-up

RECOMMENDATIONS
Basic Research & Somatic Therapy

- **Already managed under existing ethical norms and regulatory regimes at local, state, federal, national, and, for the EU, international levels**
- **Existing regulatory processes can be used to oversee basic laboratory research and somatic research and uses**
- **Limit clinical trials or therapies to treatment and prevention of disease or disability at this time**
- **Evaluate safety and efficacy in the context of risks and benefits of intended use**
- **Somatic genome editing; efficiency, specificity and off-target events, must be evaluated in the context of the specific intended use and method. No single standard can be defined at this time.**

Enhancement

- Making changes beyond ordinary human capacities; or anything outside of treatment/prevention of disease and disability
- Significant public concern about fairness, if available only to some people, and about creating pressure to seek out enhancements
- But many other kinds of enhancement are tolerated or encouraged: Nutrition, education, cosmetic procedures
- Potential for uses of genome editing beyond therapy
  - E.G.: curing muscular dystrophy vs becoming stronger than normal
  - But the range of possible uses of approved therapies for enhancement seems limited
- Enhancement unlikely to offer benefits sufficient to offset risks at this time

RECOMMENDATIONS
Enhancement

- **Genome editing for purposes other than treatment or prevention of disease <u>should not proceed at this time</u>**
- **Do not extend genome editing to purposes other than treatment or prevention of disease without extensive public input**

Heritable Genome Editing

Achieved in animals, but there are still major technical challenges for its safe and predictable use in humans.

This will require significant further research and development before it could be considered for clinical trials.

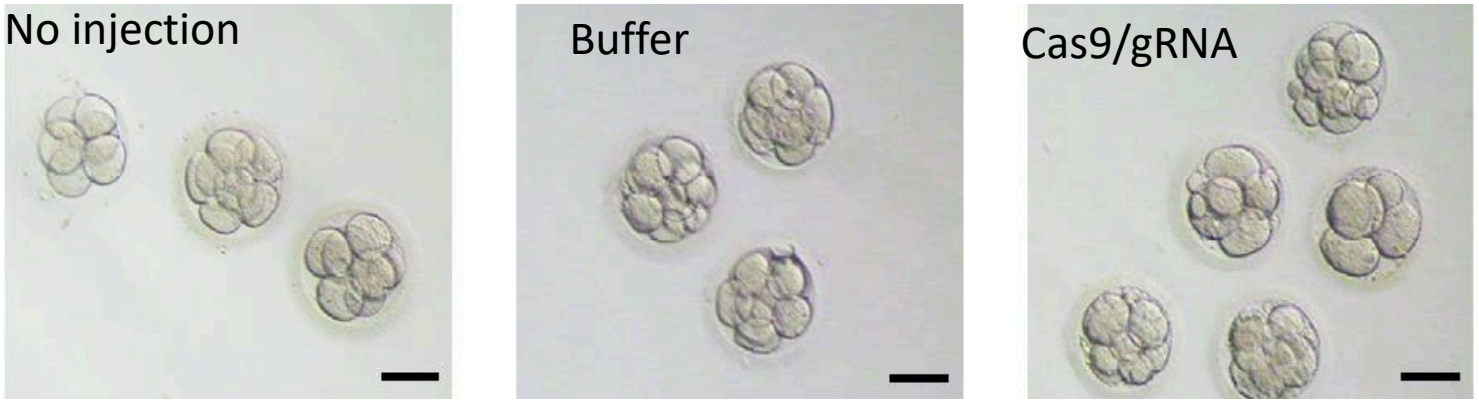
POSSIBLE METHODS:

- Editing cells that give rise to sperm, such as spermatogonial stem cells, or perhaps to eggs. Via iPS cells and in vitro-derived gametes ?
- Editing the fertilised egg (zygote). (Perhaps coincident with ICSI ?)

- The first method allows verification of the edits
- The second is more difficult to verify and currently carries a risk of mosaicism (where not all cells in the embryo carry the desired genetic alteration).

Tang, …Liu. (2017). CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. Mol Genet Genomics. (online 01/03/17)

- "CRISPR/Cas9 is effective as a gene-editing tool in human 2PN zygotes."
- "By injection of Cas9 protein complexed with the appropriate sgRNAs and homology donors into one-cell human embryos, we demonstrated efficient homologous recombination-mediated correction of point mutations in HBB and G6PD."
- "However, our results also reveal limitations of this correction procedure and highlight the need for further research."



Day 3 after injection

Heritable Genome Editing: Concerns

- Genetic changes may be inherited by the next generation
- Commonly viewed as unacceptable in the past:
  - multigenerational risks (but also possible benefits)
  - need for (and possible difficulty of) long term follow-up
  - lack of consent by affected persons (future child; generations)
  - the degree of intervention in nature
  - affecting acceptance of children born with disabilities
  - a step toward enhancement for “designer babies”

Heritable Genome Editing

- In light of recent advances, it is now a realistic possibility; therefore we need a fresh look at earlier views
- Interest driven by the thousands of inherited diseases
- Would allow individuals to have genetically related children without passing on a known risk of genetic disease
  - In many cases, preimplantation genetic diagnosis is an alternative
  - In many cases, prenatal diagnosis and selective termination is an alternative
    - But for some, these alternatives are unacceptable
- In some cases, there are no alternatives that retain the parental genetic connection
  - For example, a parent who is homozygous for a Huntington's disease gene variant

PGD is not always possible, and it is often inefficient:

- Rare individuals homozygous for any dominant version of a gene that leads to disease.
- Rare occasions where both parents are homozygous for a recessive mutation leading to a genetic disease.
- Where mutations affect fertility: too few embryos and patients might have to go through many rounds of treatment to find a disease free embryo if ever.
- For “saviour siblings”, or where more than one harmful mutation or variant allele makes the probability of finding a “disease-free” embryo very low.

The genome editing methods may turn out to be more efficient and perhaps more reliable than PGD.

And for some people they may be more acceptable, because embryos are “rescued”, not destroyed.

Heritable Genome Editing - Regulations

- Regulations covering laboratory work and human subject protections in clinical trials are applicable.
- If done in the USA with embryos (as opposed to gametes), it would be prohibited in some states; at a federal level there are restrictions on funding.
- At this time, clinical trials are not possible in U.S. due to limitations on FDA authority.
- Other countries vary, from prohibition, including much of Europe, to possible authorization under strict regulation.
- In the UK it would require a change in the HFE Act via primary legislation.

Heritable Genome Editing Clinical Trials

- Caution is needed, but being cautious does not mean prohibition.
- Heritable genome editing research trials might be permitted, but only after:
  - much more research to meet existing risk/benefit standards,
  - under strict oversight, and
  - restricted to specific set of criteria.

Criteria to Initiate Clinical Trials

- Absence of reasonable alternatives;
- Restriction to prevention of a serious disease or condition;
- Editing only genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition;
- 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;
- Availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures;

Criteria to Initiate Clinical Trials

- 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;
- 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; and
- Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

Public Engagement

> 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.

- For laboratory research and gene therapy, there are existing mechanisms that provide opportunities for public engagement.
- For somatic cell editing, public policy debates should precede any clinical trial use beyond treatment or prevention of disease and disability.
- For heritable editing, public input should precede any clinical trial.

Key Messages of Report

- Genome editing in the context of basic research and somatic gene therapy is valuable and adequately regulated.
- Somatic therapy should be used only for treatment and prevention of disease and disability; it should not be tried for enhancement at this time; public engagement and input is needed.
- Heritable genome editing needs more research before it might be ready to be tried; also, public input and engagement needed.
- When tried, heritable genome editing must be approached cautiously: used only for treating or preventing severe diseases (no enhancement), and according to strict criteria with stringent oversight.