The Need for an International Moratorium on Clinical Uses of Human Germline Gene Editing

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
ASGCT Policy Summit
November 6, 2019
Advances in Gene Editing

- Powerful tools rapidly becoming ubiquitous
- Ease, precision of technology makes experiments feasible that were too difficult to conduct using older techniques
- Improvements continue to extend applications – see “prime editing”
Gene-Editing Advance Puts More Gene-Based Cures Within Reach

Posted on November 5th, 2019 by Dr. Francis Collins

There's been tremendous excitement recently about the potential of CRISPR and related gene-editing technologies for treating or even curing sickle cell disease (SCD), muscular dystrophy, HIV, and a wide range of other devastating conditions. Now comes word of another remarkable advance—called "prime editing"—that may bring us even closer to reaching...
Advances in Gene Editing

- Powerful tools rapidly becoming ubiquitous
- Ease, precision of technology makes experiments feasible that were too difficult to conduct using older techniques
- Improvements continue to extend applications – see “prime editing”
- Multiple Applications
  - Basic Science
  - Gene Drives – the end of malaria?
  - Somatic Cell Gene Therapy – non-heritable
Somatic Cell Genome Editing Program

- *In vivo* human applications require safe, effective delivery of editing tools to *specific cell types* for *specific diseases*
- New NIH program speeds their development, supporting:
  - New delivery systems
  - Expanding repertoire of genome editors
  - Animal reporters & testing centers
  - Assessing unintended biological effects
  - Dissemination & coordinating center
NIH/Bill and Melinda Gates Foundation (BMGF) Cures Collaboration

Will invest at least $200M* over next four years to develop affordable, gene-based cures for HIV, sickle cell disease (SCD)

- Gene-based treatments
  - Dramatic advances in last decade offer extraordinary opportunities
  - However, most treatments are complex, costly ... and not yet available for most diseases
  - Potential for in vivo gene editing approach holds enormous promise

- NIH/BMGF collaboration will
  - Identify potential candidate cures for HIV, SCD for pre-clinical and clinical evaluation
  - Work with African partners to advance promising candidates to late-phase clinical trials

*All $ amounts in U.S. dollars
Research Focus of the NIH-BMGF Collaboration

- Sustained remission strategies
- Vaccinal effect
- Home assays detecting viral load

- Shared Gene-based Strategies
  - Vector tropism and efficiency
  - Gene targeting
  - \textit{In vivo} delivery

- SCD
  - Epidemiology
  - Point of care diagnostics
  - Pilot infant screening
  - Guideline-based care for infants with SCD

- NIH-BMGF Collaboration
Advances in Gene Editing

- Powerful tools rapidly becoming ubiquitous
- Ease, precision of technology makes experiments feasible that were too difficult to conduct using older techniques
- Improvements continue to extend applications – see “prime editing”
- Multiple Applications
  - Basic Science
  - Gene Drives – the end of malaria?
  - Somatic Cell Gene Therapy – non-heritable
- Human Germline Modification – heritable
  - Profound ethical implications
On the Ethics of Human Germline Editing in the Era of CRISPR

- 2015:

Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight. It would be irresponsible to proceed with any clinical use of germline editing.

*The New York Times*

*Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited*
On the Ethics of Human Germline Editing in the Era of CRISPR

- 2015: International Summit on Human Gene Editing
- 2017:

Germline (Heritable) Genome Editing

- Permit clinical research trials only for compelling purposes of treating or preventing serious disease or disabilities, and only if there is a stringent oversight system able to limit uses to specified criteria
- Ongoing reassessment and public participation should precede any heritable germline editing
We conclude that the use of heritable genome editing interventions to influence the characteristics of future generations could be ethically acceptable in some circumstances, provided:

• it is intended to secure, and is consistent with, the welfare of a person who may be born as a consequence of interventions using genome edited cells; and

• it upholds principles of social justice and solidarity, i.e. it should not be expected to increase disadvantage, discrimination, or division in society.
On the Ethics of Human Germline Editing in the Era of CRISPR

- 2015: International Summit on Human Gene Editing
- 2018: “Genome Editing,” Nuffield Council of Ethics (UK)
- November 2018: Second International Summit on Human Genome Editing
“This work represents a deeply disturbing willingness by Dr. He and his team to flout international ethical norms… Lest there be any doubt, and as we have stated previously, NIH does not support the use of gene-editing technologies in human embryos.”

“While we … applaud the rapid advance of somatic gene editing into clinical trials, we continue to believe that proceeding with any clinical use of germline editing remains irresponsible at this time.”
On the Ethics of Human Germline Editing in the Era of CRISPR

- December 2018: WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing
- 2019: International Commission on Clinical Use of Human Germline Genome Editing—U.S. National Academies of Sciences and Medicine, Royal Society of the United Kingdom
Legal and Regulatory Prohibitions on Human Germline Gene Editing: The International Landscape

- Legislation
- Regulatory

Singapore
Legal and Regulatory Prohibitions on Human Germline Gene Editing: The International Landscape

- ~30 countries have legislation or regulations that directly or indirectly prohibit clinical uses of germline editing*
- Prohibitions embedded in several important international instruments:
  - UNESCO Universal Declaration on the Human Genome and Human Rights (1997)
  - Council of Europe's Convention on Human Rights and Biomedicine (1997)
- Scope of any future clinical applications involving human germline editing usually would require legislation allowing certain procedures

*From HIROs (Heads of International Research Organizations) survey and broader research
Current Justification for a Moratorium?

- Safety: risk of unintended mutations ("off-target edits")
- Medical: are there needs that only germline editing could meet?
  - Currently editing would require use of *in vitro* fertilization
  - Genetic diagnosis of embryos would then be needed
  - Why not just implant the unaffected embryos?
  - Mitochondrial diseases are in a different category
- Societal, ethical, moral issues
  - Consent
  - Justice/equity
  - Philosophical
  - Theological
COMMENT

Adopt a moratorium on heritable genome editing

Eric Lander, Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg and specialists from seven countries call for an international governance framework.

THE NIH DIRECTOR

March 13, 2019

NIH supports international moratorium on clinical application of germline editing

Today, leading scientists and ethicists from seven countries have called for an international moratorium on the use of genetic editing to modify the human germline for clinical purposes. The call comes in the wake of irresponsible and unethical research in China, in which twins were born after alterations to their DNA before implantation. This unexpected and unwelcome revelation rolled the scientific community and the general public, and crystallized the need for guiding international principles. Research on the potential to alter the very biological essence of humanity raises profound safety, ethical, and philosophical issues. I expressed NIH’s position on the incident in November 2018.
We assert that germline gene editing is currently inappropriate in human clinical settings.
We must never allow our technology to eclipse our humanity.