Regulatory Guardrails for Human Gene Editing

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Advisory Panel to Better Understand and Make Recommendations Regarding the Implications of Genome-editing Technology for the Citizens of the State

Augusta, Maine

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Outline:

1. United States – Federal
   A. Human Subjects Research – Institutional Review Boards
   B. Gene editing laws and regulations
2. United States – State Statutes
3. International

Distinction

Somatic Human

- Edited genes not passed to offspring
- Numerous disease directed clinical and preclinical trials
- Tech rapidly advancing, e.g., base editing, prime editing
- Ethical issues of human subjects research

Heritable (Germline) **Human**

- Edited genes passed to offspring
- In-vitro fertilization, typically
- Embryo cells edited, different risks to human subject
- Off target effects have longer reach

- **Further Distinction:**
  - Germline for research
  - Germline for reproduction

1.A Institutional Review Boards

- History
- Current Practice
- Jesse Gelsinger

Nuremberg Code -- Background

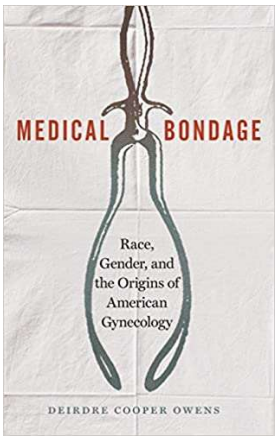
- Nazi atrocities included experimentation on concentration camp inmates
- Defense at the Nuremberg trials include the claims that German research practices were not substantially different than practices in other countries and that there is no published standard to follow
- The Nuremberg Code, written by Leo Alexander (Tufts University), was included in the tribunal's decision give presented the standard protections of human subjects
- The Nuremberg Code survives as an important document which states the ethical principles underlying the protection of human subjects

Nuremberg Code - Principles

- The voluntary consent of human subjects is absolutely essential
- The experiment should…yield fruitful results for the good of society
- Conducted so as to avoid all unnecessary physical and mental suffering
- No experiment will be conducted…where it is likely that death or disabling injury will occur…
- During the experiment …the subject should be at liberty to bring the experiment to an end…

Anarcha, Betsy and Lucy and vesicovaginal fistula, 1845

- J. Marion Sims, 1813-1883, South Carolina, Alabama, New York, Europe
- Sims speculum, Sims sigmoid catheter, Sims' positon, silver wire as suture. James Garfield, Woman's Hospital in NYC
- 1845-1849, experimental surgery on 8 to 12 women who were enslaved. Repeated surgeries (30 for Anarcha)
  - Sought women with condition from owners of slaves; paid owners to rent them; consent from owners.
  - White medical assistants/apprentices quit after a time; trained enslaved women to assist
  - Anesthesia not used (myths about pain sensitivity of persons with African ancestory; newness of anesthesia)

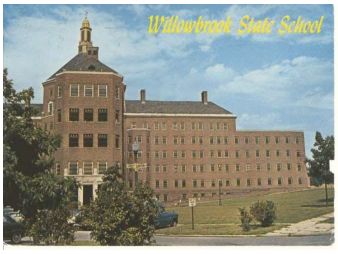


Dr. Cooper Owens Lecture: youtube.com/watch?v=op12iUfBFXo

Tuskegee Syphilis Study

- 1930 until 1972
- US Public Health Service
- Poor, African-American men in Macon County, Alabama
- "Study in nature" of syphilis
- Prevented subjects from seeking treatment in order to study untreated syphilis
- Little disclosure; deceptive language

Willowbrook Hepatitis Research, 1950-70



- 60 children (potentially an undercount) intentionally infected with Hepatitis to study effects of potential therapeutic agent.
- Saul Krugman, MD, well known for
  - Identification of Hepatitis A and B
  - Immunoglobulins confer passive immunity
- During some periods, children denied admission to Willowbrook unless they consented to the research study
- Disclosure about the study was misleading
- Some defend research: although children were intentionally infected, they probably would have been infected anyway, and they received good clinical care because they were part of the study

Research Ethics Documents

- Nuremberg Code, 1947
- Declaration of Helsinki, 1964
- National Research Act, 1974
- Belmont Report, 1978
- Common Rule, 1991
- Code of Federal Regulations (CFR)

Belmont Report, 1978

- Respect for Persons: Potential subjects decide whether to participate in research
- Beneficence: Researchers must protect the welfare of subjects
- **Justice: No group has preferential access to benefits of research; no group disproportionately burdened by research**

Institutional Review Boards

- Established by National Research Act, 1974
- 45 CFR 46, Common Rule, 1991
- Charged with ethical review of human subject research
- Membership must be diverse and community specific: scientist, nonscientist, community person
- Local boards familiar with local norms

IRB Responsibilities

- Informed consent
- Study design
- Subject selection
- Safety monitoring
- Confidentiality

Informed Consent – required disclosures

- Subjects know they are involved in research
- Right to decline participation
- Nature of research
- Risks and discomforts
- Benefits
- For therapeutic trials, alternatives to participating in study
- Right to withdraw

Study Design

- Study must make a contribution to knowledge
- Balance risks to subjects against knowledge gained
- IRB evaluates study design
  - Is the topic important?
  - Is the research design adequate?

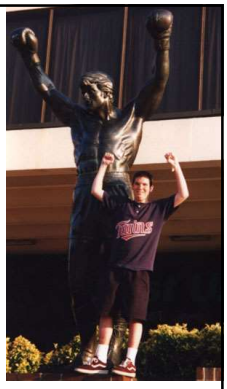
Subject Selection

- Fairness
  - No group disproportionately bears the burdens of research
  - Benefits of research open to all (No group disproportionately receives benefits of research)
- Vulnerable populations protections
  - Children
  - Mentally ill
  - Incarcerated

Shifts in Clinical Research

- **Increase in number**
  - In 2006, 59,000 clinical trials (50% increase from 2000)
- **Shift in sponsorship**
  - In 1991, 80% sponsored by federal government or nonprofits
  - In 2008, more than 50% sponsored by industry
- **Shift in who is running trials**
  - Away from academic medical centers
  - Toward for profit companies
  - Managed by Contract Research Organizations (CROs): 28% in 1993, 64% in 2003
  - Data resides in central office (often a for-profit company)
- **Shift in IRB approval of trials**
  - Away from university IRBs
  - Toward for-profit IRBs
  - Western IRB reviews more than half of FDA drug trials
  - NIH requires a single IRB for multisite trials

Jesse Gelsinger



- 18 y.o. with Ornithine Transcarbamylase Deficiency (OTC) who died after participating in gene therapy research at U Penn, 1999.
- OTC is a rare X-linked genetic disorder resulting in disruption of the urea cycle. OTC results in excess ammonia after ingesting protein.
- Edited genes were delivered by an adenovirus vector, which likely triggered a harmful immune response.
- Irregularities with consent
  - Family thought trial was for treatment, not safety
  - Informed consent omitted data on animal deaths
  - Previous adverse reactions not reported to FDA by Penn and others
  - At time of trial, Jesse's elevated LFT's (and perhaps fever) should have disqualified him
- Financial ties
  - James Wilson directed **Institute for Human Gene Therapy** at Penn
  - James Wilson founder of **Genovo**, private company, which had a financial interest in the therapy
  - Genovo contributes a quarter of IHGT's 22 million dollar budget
- Death and subsequent investigation led to near moratorium on further gene editing research.

Therapeutic Misconception

- The tendency to overestimate the benefits of an experimental therapy (patients, families and researchers). For example, a parent's belief that an agent in a phase 1 toxicity trial has a good chance of curing a child's advanced cancer.
- Further, patients and families may ignore the fact that research imposes burdens not present in clinical medicine, and that some aspects of a study might not be in their best interest (e.g., randomization).
- Therapeutic misconception also occurs when subjects inaccurately believe that the research protocol involves individualized treatments selected primarily for their benefit.
- Generally speaking, therapeutic misconception may undermine a subject's ability to provide informed consent, a necessary condition for trial participation.

Kimmelman J. The therapeutic misconception at 25: treatment, research, and confusion. Hastings Cent Rep. 2007 Nov-Dec;37(6):36-42.

1.B Federal Laws

Cloning

- There is no Federal law prohibiting cloning.
  - Multiple bills introduced since Dolly the sheep was cloned in 1997
  - General disagreement whether to ban cloning to produce a human being and also cloning for biomedical research.
- FDA used its regulatory power to require that "cloning technology to create a human being" apply to the agency for permission, The FDA made it clear that "there are major unresolved safety questions" such that they would turn down any application.
- Theoretically, a private company (not using Federal funds) could perform cloning experiments, but they would not be able to market therapies given need for FDA approval.

Cloning, State Laws

- Arizona, Arkansas, Michigan, North Dakota, Oklahoma, South Dakota, and Virginia prohibit both cloning to produce children and cloning for biomedical research.
- California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, Missouri, Montana, New Jersey, Rhode Island prohibit cloning-to-produce-children while permitting cloning-for-biomedical-research.
- Minnesota appears to prohibit cloning for research, but is silent on cloning to produce children.
- Maine, silent on cloning, but prohibits research on intrauterine or extrauterine fetuses. Maine Revised Statutes Title 22 §1593, (2003)

Heritable (Germ Line) Gene Editing, Federal

- 1995, Dickey-Wicker amendment (appropriations rider) prohibits use of HHS funds for the creation of human embryos for research or for research in which human embryos are destroyed (H.R. 2880, Sec. 128).
- 2015: NIH (Francis Collins statement) says it will not fund any use of gene-editing technologies in human embryos, citing
  - serious and unquantifiable safety issues,
  - ethical issues presented by altering the germline in a way that affects the next generation without their consent
  - current lack of compelling medical applications justifying the use of CRISPR/Cas9 in embryos.
- 2016: Congress bars FDA (in an appropriations rider) from approving clinical trials "in which a human embryo is intentionally created or modified to include a heritable genetic modification"
- 2020: Language briefly removed by Democrats, who thought the prohibition was too broad, potentially banning mitochondrial research. Ban eventually restored.

NIH Statement: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human_embryos#:~:text=However%2C%20NIH%20will%20not%20fund,that%20should%20not%20be%20crossed. Downloaded Sept 2022

3. International

laws, agreements, reports

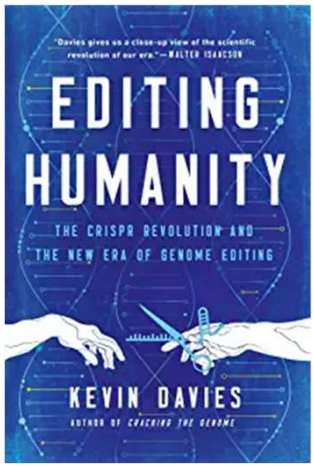
Cloning International

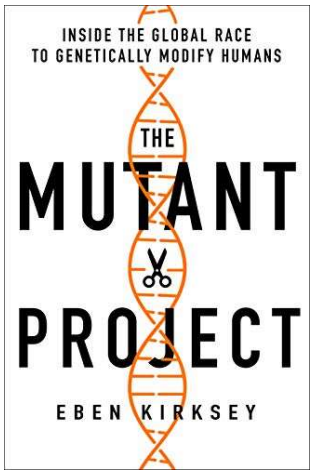
- 1997, Council of Europe *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (the Oviedo Convention) Banned cloning and germline gene editing. Eventually ratified by 29 countries.
- 2002, Germany bans "as a matter of principle, the importation and utilization of embryonic stem cells" as well as the derivation of stem cells.
- 2004, Canada, "No person shall knowingly create a human clone by using any technique," and barred payment to providers of sperm, eggs, or embryos.
- 2004, Italy, illegal to create human embryos for research.
- By 2005 approximately thirty countries banned human cloning.
- 2005, United Nations General Assembly adopted a declaration calling member nations to "prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life." Eventually ratified by 84 countries, including the United States. Countries to vote against the measure included the United Kingdom, India, and South Korea.

United Nations General Assembly, Fifty-ninth session, Resolution 59/280
"United Nations Declaration on Human Cloning" (March 8, 2005)

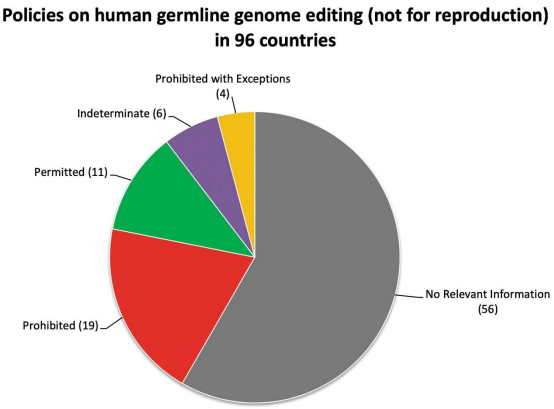
Dr. He Jiankui

- 2018 Clinical Trial
- Aimed at conferring immunity to HIV
- 3 live births
- 2 born prematurely at 31 weeks
- Trial reported by MIT tech review, prior to formal announcement/publication
- Dr. He announced/defended his trial at conference the next day
- Criticized by scientific community
- Imprisoned in China (3 year sentence)



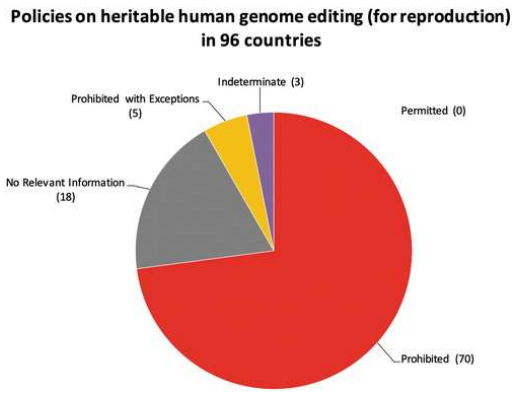


International – Gene Editing Research



Françoise Baylis, Marcy Darnovsky, Katie Hasson, and Timothy M. Krahn. Human Germline and Heritable Genome Editing: The Global Policy Landscape. *The CRISPR Journal*. Oct 2020.365-377.http://doi.org/10.1089/crispr.2020.0082

International – Gene Editing Reproduction



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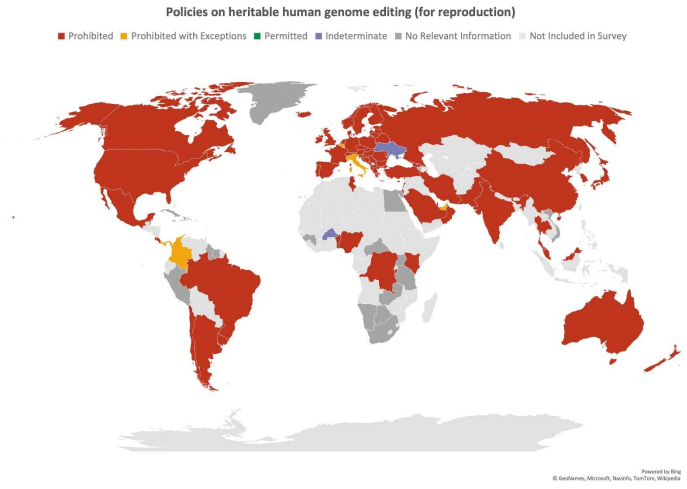

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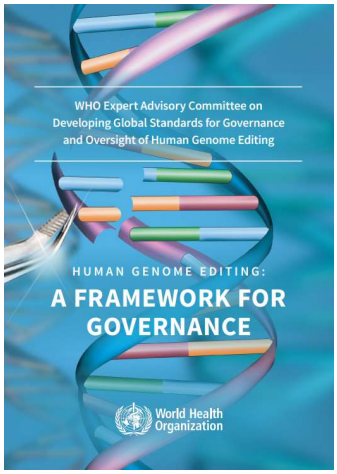
WHO Human Gene Editing Reports 2021

- 3 Reports: Human Recommendations; Position Paper; A Framework for Governance
- Somatic and Human Heritable
- "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing."
- 9 process and governance recommendations

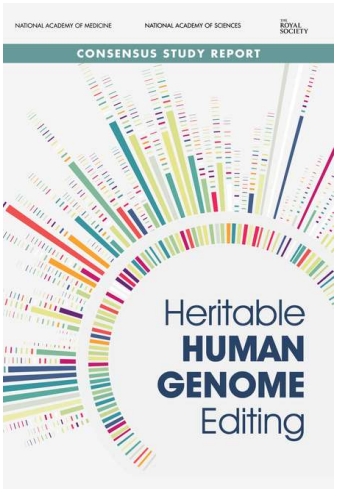


Recommendations of the Committee on the governance and oversight of human genome editing

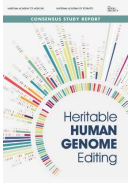
1. Leadership by the WHO and its Director-General
2. International collaboration for effective governance and oversight
3. Human genome editing registries
4. International research and medical travel
5. Illegal, unregistered, unethical or unsafe research and other activities
6. Intellectual property
7. Education, engagement and empowerment
8. Ethical values and principles for use by WHO
9. Review of the recommendations (within 3 years)

National Academy of Medicine, National Academy of Sciences, Royal Society, 2020

- Heritable Human Only
- 11 recommendations
- **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.



Recommendations 2-4



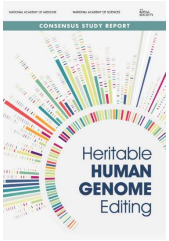
2: Extensive societal dialogue should be undertaken ….

3: It is not possible to define a responsible translational pathway applicable across all possible uses of HHGE… Clinical use of HHGE should proceed incrementally.

4: Initial uses of HHGE …should…meet all of the following criteria:

a) the use of HHGE is limited to serious monogenic diseases; …
b) the use of HHGE is limited to changing a pathogenic genetic variant known to be responsible for the serious monogenic disease …
c) no embryos without the disease-causing genotype will be subjected to the process of genome editing…; and
d) 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… or (ii) have extremely poor options, because the expected proportion of unaffected embryos would be unusually low, … and have attempted at least one cycle of preimplantation genetic testing without success.

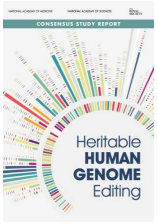
Recommendations 5-6



5: Before any attempt to establish a pregnancy with an embryo that has undergone genome editing, preclinical evidence must demonstrate that HHGE can be performed with sufficiently high efficiency and precision to be clinically useful. …

6: Any proposal for initial clinical use of HHGE should meet the criteria for preclinical evidence set forth in Recommendation 5. …

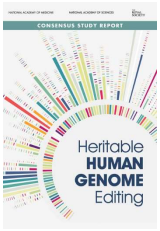
Recommendations 7-8



7: Research should continue into the development of methods to produce functional human gametes from cultured stem cells. …However, the use of such in vitro–derived gametes in reproductive medicine raises distinct medical, ethical, and societal issues that must be carefully evaluated…

8: Any country in which the clinical use of HHGE is being considered should have mechanisms and competent regulatory bodies to ensure that all of the following conditions are met...

Recommendations 9-11
(International Panels)



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). …

10: In order to proceed with applications of HHGE that go beyond the translational pathway … an international body with appropriate standing and diverse expertise and experience should evaluate and make recommendations concerning any proposed 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.

Thank You

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