



Genome Editing and Human Reproduction

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Genome Editing in Relation to Reproduction

- Is human somatic cell genome editing ok? (idea that not heritable and not involved in reproduction not necessarily true, though has many non-reproductive possible clinical applications)
- Is human germline genome editing ok? (eggs, sperm, embryos) ok for research purposes?
- Is reproduction using edited human germ cells or embryos ok?
- When are fertility clinics involved? Egg, sperm, embryo, or somatic cell harvesting or pluripotent stem cell derivation for genome editing treatment; implantation / reproduction using any of these products following genome editing; also source of gametes and embryos for research and possible site of clinically relevant research
- *Proof of principle scientific papers:*
- Liang et al, October 2015, Protein & Cell, CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes (human embryos can be edited using CRISPR/CAS9 system)
- Hikabe et al, October 2016, Nature, Reconstitution in vitro of the entire cycle of the mouse female germ line (in mouse model, eggs and embryos were derived from somatic cells via induced pluripotent stem cells, embryos were implanted, live births resulted; in other words, somatic cells can lead to heritable genetic modification, too)

Regulating Human Genome Editing (image opposite from Nature, 2015)

In Europe, editing of germ cells or embryos in a clinical context is mostly prohibited.

In the UK, human eggs, sperm, and embryos (up to 14 days old) can be edited in a research context after review by the HFEA that the research is justified and has been supported by rigorous scientific and ethical review (Kathy Niakan at Crick got a license from HFEA to work with leftover IVF embryos for research purposes only)

In many places, editing of somatic cells is regulated differently, e.g. in the UK they are regulated by the Human Tissue Authority

In Canada, genome editing of human embryos is prohibited by legally binding law

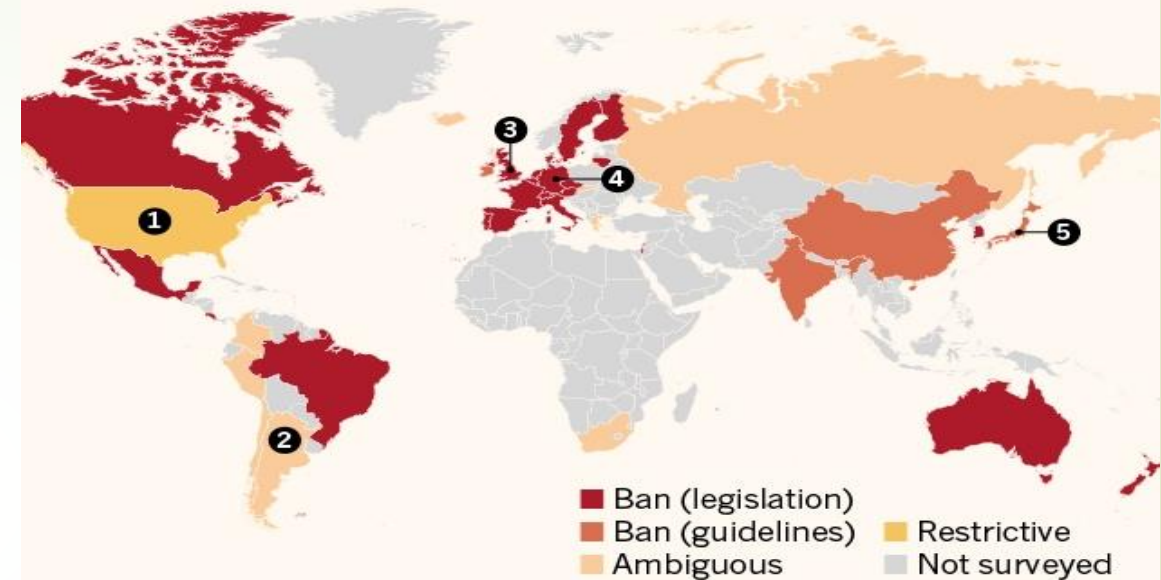
In the US, federal research funds cannot be spent on editing human embryos but that leaves privately funded and some state funded research. At the December 2015 International Summit on Human Gene Editing (where I was a speaker), jointly sponsored by the AAS, UK's Royal Society, and China's Academy of Sciences, the organizers issued a statement on the last day calling it irresponsible to proceed with human germline editing without "broad societal consensus"

In China, where the research for the first papers published on the editing of human embryos was carried out, the prohibition is a guideline rather than legally binding; the researchers avoided the guideline by using non-viable embryos

In October 2015, UNESCO recommended moratorium on germline human genome editing

CRISPR EMBRYOS AND THE LAW

Regulations governing genetic modification in human embryos vary. Some countries ban the practice through legislation that carries criminal penalties; others have unenforceable guidelines.



1. THE UNITED STATES does not allow the use of federal funds to modify human embryos, but there are no outright genome-editing bans. Clinical development may require approval.

2. ARGENTINA bans reproductive cloning, but research applications of human-genome editing are not clearly regulated.


3. THE UNITED KINGDOM's independent Human Fertilisation and Embryology Authority may permit human-genome editing for research, but the practice is banned in the clinic.

4. GERMANY has strict laws on the use of embryos in assisted reproduction. It also limits research on human embryos, and violations could result in criminal charges.

5. JAPAN, like China, India and Ireland, has unenforceable guidelines that restrict the editing of a human embryo's genome.

Nuffield Council on Bioethics Working Group on Genome Editing

- Our report, **Genome Editing: An Ethical Review**, was launched on October 6th, 2016.
- Editing metaphor – makes it seem very precise, and as if there is a knowledgeable editor, suggesting that safety and accuracy are likely to be high and off-target effects minimal
- Public interest in genome editing - we drew out the societal stakes, which are particularly important from the perspective of clinical fertility medicine which tends to take an individualistic, bioethical perspective rather than thinking about distributive issues like access and health disparities and the effect of medicalizing and pathologizing and deselecting variation
- We warned against the consumerization of reproduction, where public debate is non-existent and instead each new step is simply another upgrade within fertility clinics; this leads to so-called 'liberal' eugenics, and might make it impossible to prevent the drift to trait deselection and designer babies
- Social justice and a just society should be equal goals with patient imperatives to benefit from the fruits of research and the right to have a genetically related health child
- Law and public policy are important: the relation between public and private, resolving conflict, and seeking common values
- Unintended consequences, success and failure
- Setting of legal limits and regulatory environments



Phase 2: Normative guidelines for human genome editing (currently researching)

- ▶ Some possible framing recommendations, from my perspective:
- ▶ -make sure that people know that somatic as well as germline genome editing can lead to reproduction and heritable genetic modification
- ▶ -set up monitoring and mitigation for drift to becoming an unacceptably selecting society before moving ahead with human genome editing
- ▶ -disability justice and rights perspectives cautioning against rabid medicalization and deselection need to accompany pro-cures patient advocacy; it is too easy to start to treat patient advocates as a cheerleading squad for undertaking procedures for which ethical, social, and / or scientific issues remain
- ▶ -we also need good data on current clinical practice: for what conditions do we consider embryos non-viable, or an abortion therapeutic? How has it changed over time as preimplantation and prenatal screening and diagnosis has improved? Does this data reveal a pattern, as reported anecdotally of a trend to more and more reasons of less and less severity for deselection?
- ▶ -set social justice and equity goals and means of monitoring them, attending especially to racial, gender, class, and north-south equity, where health inequities tend to congregate

Range of positions from Summit summarized in my talk (the positions I personally favor are in italics)

- ▶ ***“Yes” to human germline genome editing, in order from the most to the least permissive:***
- ▶ Edit the human germline genome for reproduction if it is no more risky than “natural” sexual reproduction and is aimed at eliminating serious genetic conditions.
- ▶ Edit the human germline genome for reproduction if it is likely to be safe, effective and make a big difference. (For example, for monogenic/oligogenic serious medical conditions.)
- ▶ *Edit the human germline genome for reproduction to avoid having offspring born with a serious condition only if there are no other alternatives, such as in vitro fertilization with pre-implantation diagnosis. (For example, if both genetic parents are homozygous for the same serious medical condition so that none of their embryos would otherwise be free of the condition.)*
- ▶ Move toward editing the human germline genome for cultural and religious reasons, such as when a given national culture is pronatalist, has a pro-medicine ethos, and has significant state subsidies for reproductive and screening technologies.
- ▶ ***“No” to human germline genome editing, in order from the most to the least permissive:***
- ▶ *Hold off (place a moratorium) on editing the human germline genome for reproduction while we work out the technical issues of safety, off-target effects, efficacy, efficiency of the edit, and the development of a clinical grade delivery mechanism for the editing system.*
- ▶ *Hold off (place a moratorium) on editing the human germline genome for reproduction at least until we (re)frame and make much more inclusive vital ethical, social, and economic debates around ableism and disability justice, the over medicalization of human variability, racism and sexism in science, local and global health inequality, the views of non-stakeholders as well as stakeholders, and the needs of future generations, the vulnerable, and other species.*
- ▶ Ban the editing of the human germline genome for reproduction because it is a reasonable line to draw against hubris and in favor of our human future, against a highly likely slide toward eugenics and the exacerbation of inequality, and against possible ecological and other harms.
- ▶ Ban the editing of the human germline genome because of the moral status of the embryo, human dignity, the freedom rights of the genome-edited child, and/ or religious conviction.