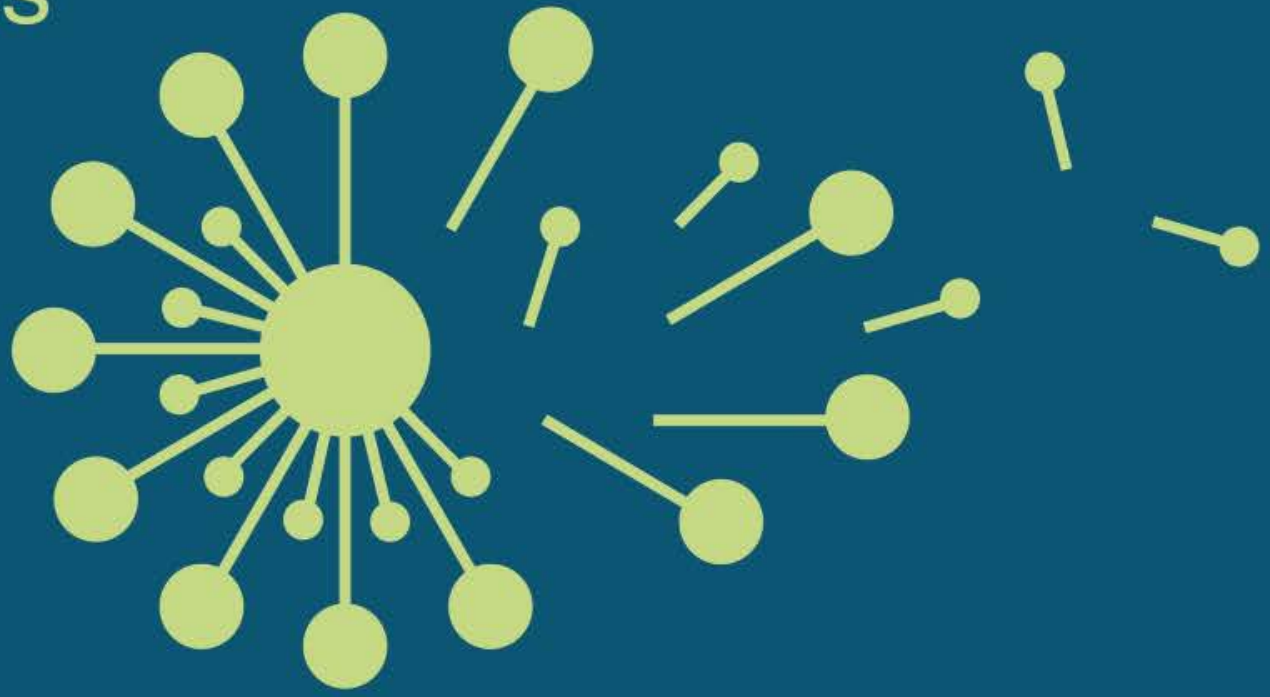
NUFFIELD COUNCIL ON BIOETHICS

Genome editing and human reproduction: social and ethical issues



Pete Mills, Assistant Director

Nuffield Council on Bioethics (UK)

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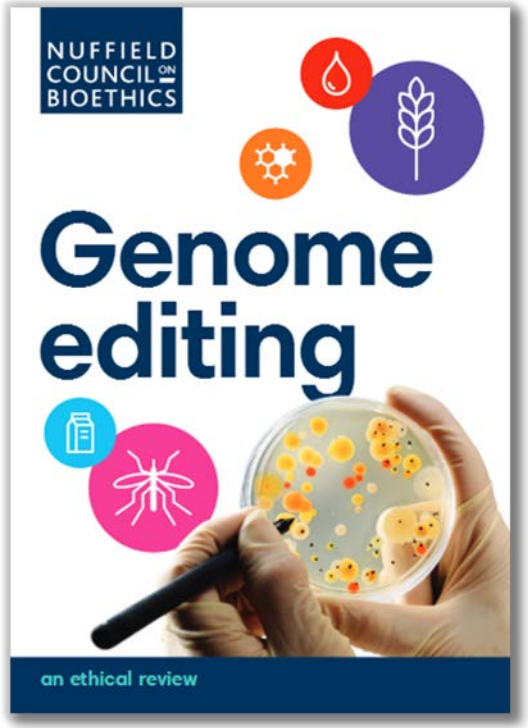
What are heritable genome editing interventions?

4.40 It clearly matters whether this potential application of genome editing is seen as a technique for treating an embryo (as a morally considerable being that, *a priori*, deserves treatment to address a medical condition) or as increasing the reproductive options available to those who know themselves to be at risk of passing on a genetic condition. Genome editing is not straightforwardly therapeutic in the way that gene therapy is therapeutic, treating an existing patient who is affected by an unwelcome condition; nor is it preventative in the way that some public health measures are preventative by addressing an imminent risk, since the risk itself can be avoided by not conceiving children. On the other hand, it *is* therapeutic, in the sense that it potentially overcomes infertility (albeit that the infertility is voluntary, a hard choice among an undesirable set of options) and it *is* preventative in that, taking the decision to reproduce as given (or, at least, one that a couple is entitled to make and should not be prevented from making), it may prevent any child they have being born with a serious or life-limiting disability. How these things are governed depends greatly on how reproductive choice is valued and the legitimate extent of society's interest in its members' choices and welfare.[198] Whether PGD or egg donation, or any of the other paths that may be available, count as alternatives to genome editing, depends on these matters of value as much as on matters of fact.



What's new?

People approach reproduction in

- novel *epistemic position* (genomic research, genetic testing)
- novel *sociotechnical conditions* (ARTs, reprogenetics… genome editing?)

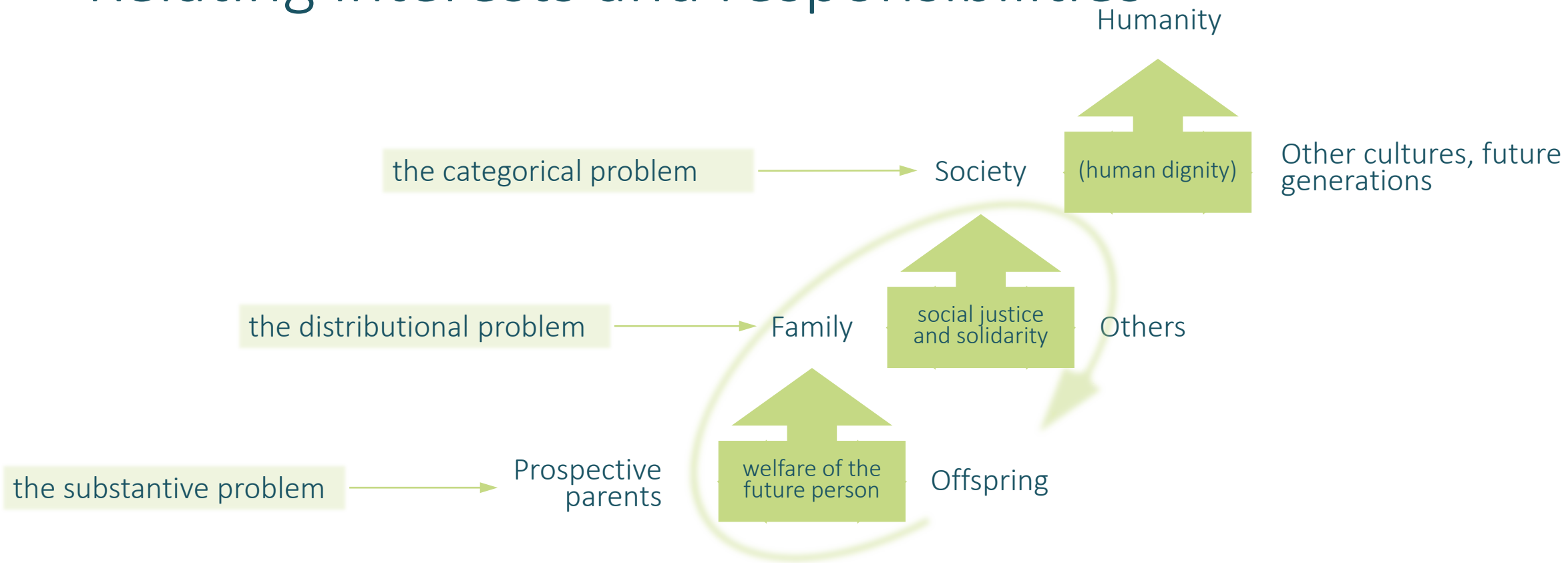
But why *genome editing*?

- Is there an unmet need?
- Isn't there a moral prohibition?

Genome editing as emerging biotechnology

- dynamic relationship between technology and norms
- transformative technology?
- *what role for moral agency?*
- *what next*?

Relating interests and responsibilities



Principles

Principle 1: The welfare of the future person

Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.

Principle 2: Social justice and solidarity

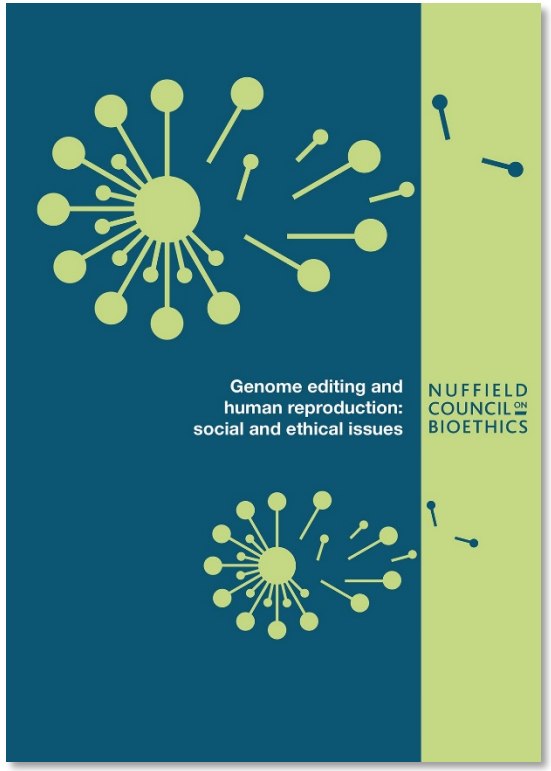
The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.

Conclusions

- Heritable genome editing interventions *could be morally permissible* in certain circumstances

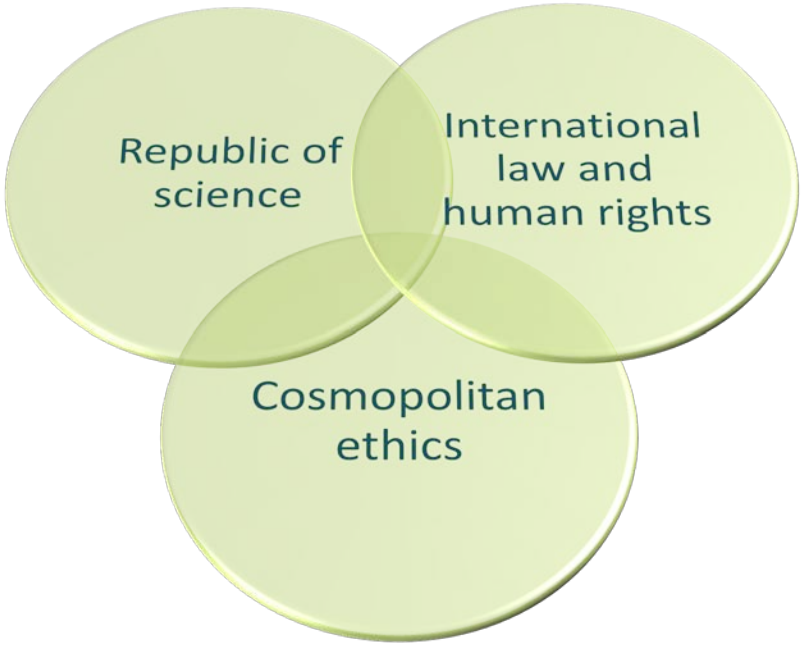
Two principles; 15 recommendations, including:

- Research and public debate are needed before legal change
- Responsible governance measures should be put in place
- Licensing and regulatory controls are essential
- Elaborate governance within human rights framework



Three venues of 'geo-ethics'

- Is there an 'international consensus'?
- Knowledge, technologies and people are highly mobile
- 'Artefacts have ethics'
- Local responses elaborate networks of interdependent moral norms, rooted in implicit knowledge and culture
- There is a need for "for international, interdisciplinary and cosmopolitan reflection on the progress of thinking on these issues around the world"



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Thank you.

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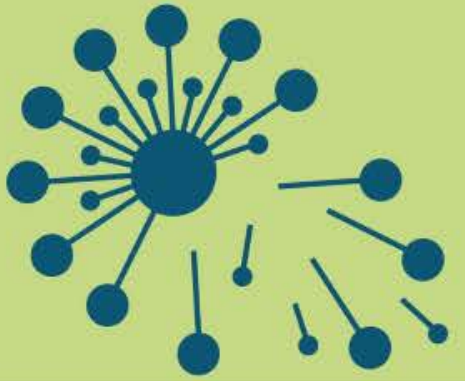
Nuffield Foundation

MRC Medical Research Council

wellcome



So: what's distinctive about the Nuffield report?

- We don't start with the *technology* (genome editing) but with the *challenge* (overcoming the givens of genetic inheritance)
- Our aim is not to protect *research* (by segregating it from clinical use) but to identify possible pathways for responsible *translation*
- We don't frame our inquiry within an implicit *medical* frame (which only asks: 'how should we treat people?') but a critical *moral* frame (which begins by asking: 'why should we treat people?')
- We don't narrow our inquiry around a particular 'permission' question ('Should we allow…?') but broaden the frame of evaluation to encompass alternative pathways (we consider the *options* as well as the *choices*)
- We do not focus only on *innovation* (the next step) but also consider technology *diffusion* and repurposing (future states of affairs that we would prefer to secure or to avoid)
- Instead of trying to bring specific cases under ambiguous abstract principles, we attend to the social dimension of how agency is situated in a contingent, dynamic context (allowing that experience can transform norms)
- We don't focus only on *instances* but also on *circumstances* (we don't think the justification for permitting human genome editing is contained in the ontology of a clinical condition but depends on the medical, social and governance context as well)
- We don't think of public debate only as instrumental for policy (to inform particular decisions) but as the condition through which society can express its interest in the conditions of common life, as implicated in a system of interrelated moral norms and values

An international consensus?

"The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity" (Universal Declaration on the Human Genome and Human Rights, Art.1)

"In the fields of medicine and biology...the prohibition of eugenic practices, in particular those aiming at the selection of persons [must be respected]" (EU Charter of Fundamental Rights, Art.3(2))

"An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." (Oviedo Convention, Art. 13)

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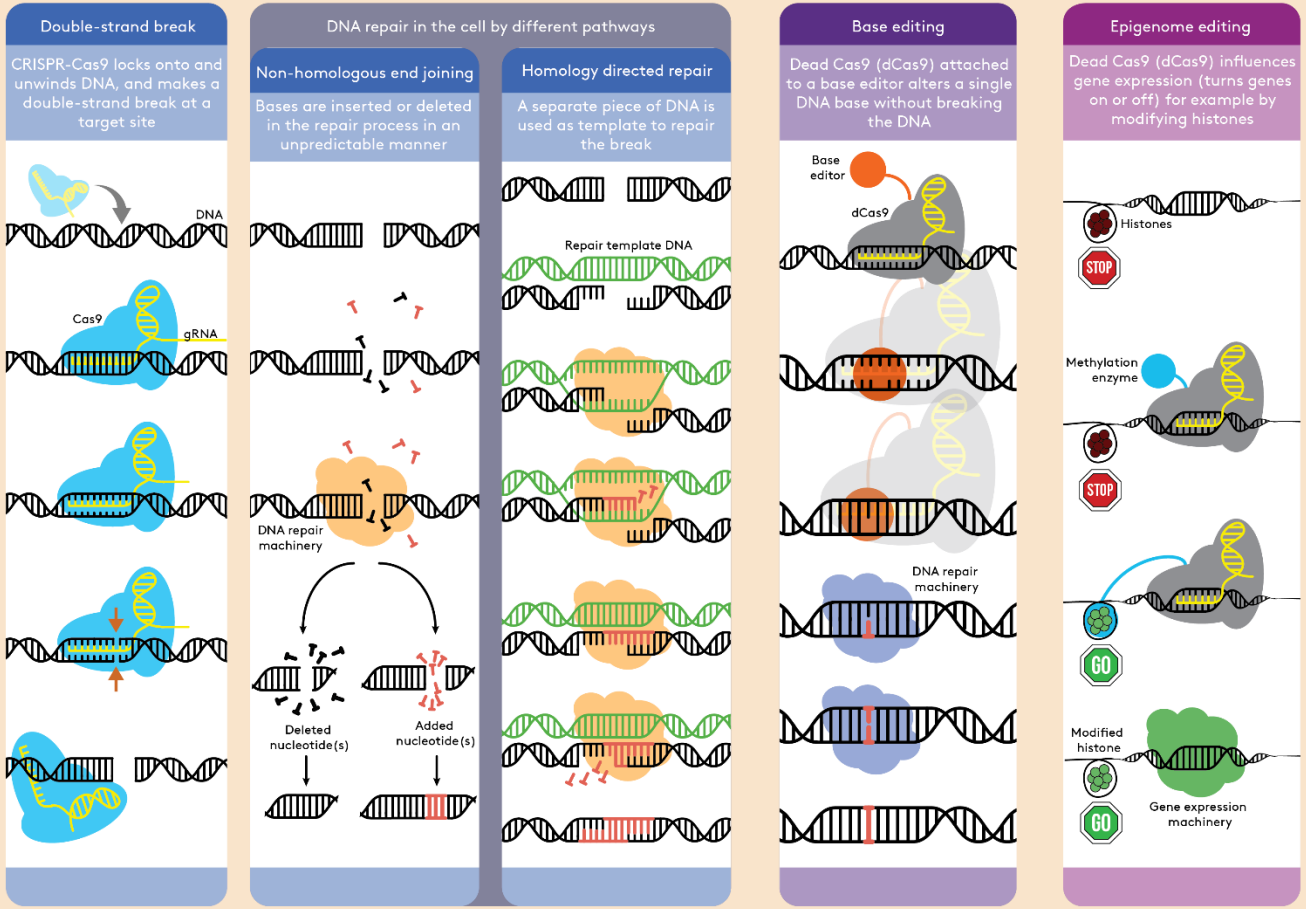
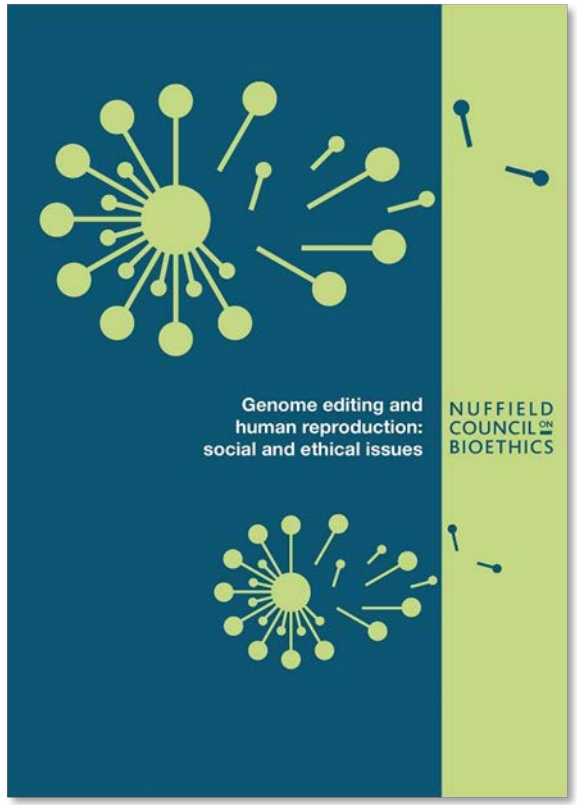
Genome editing mechanisms





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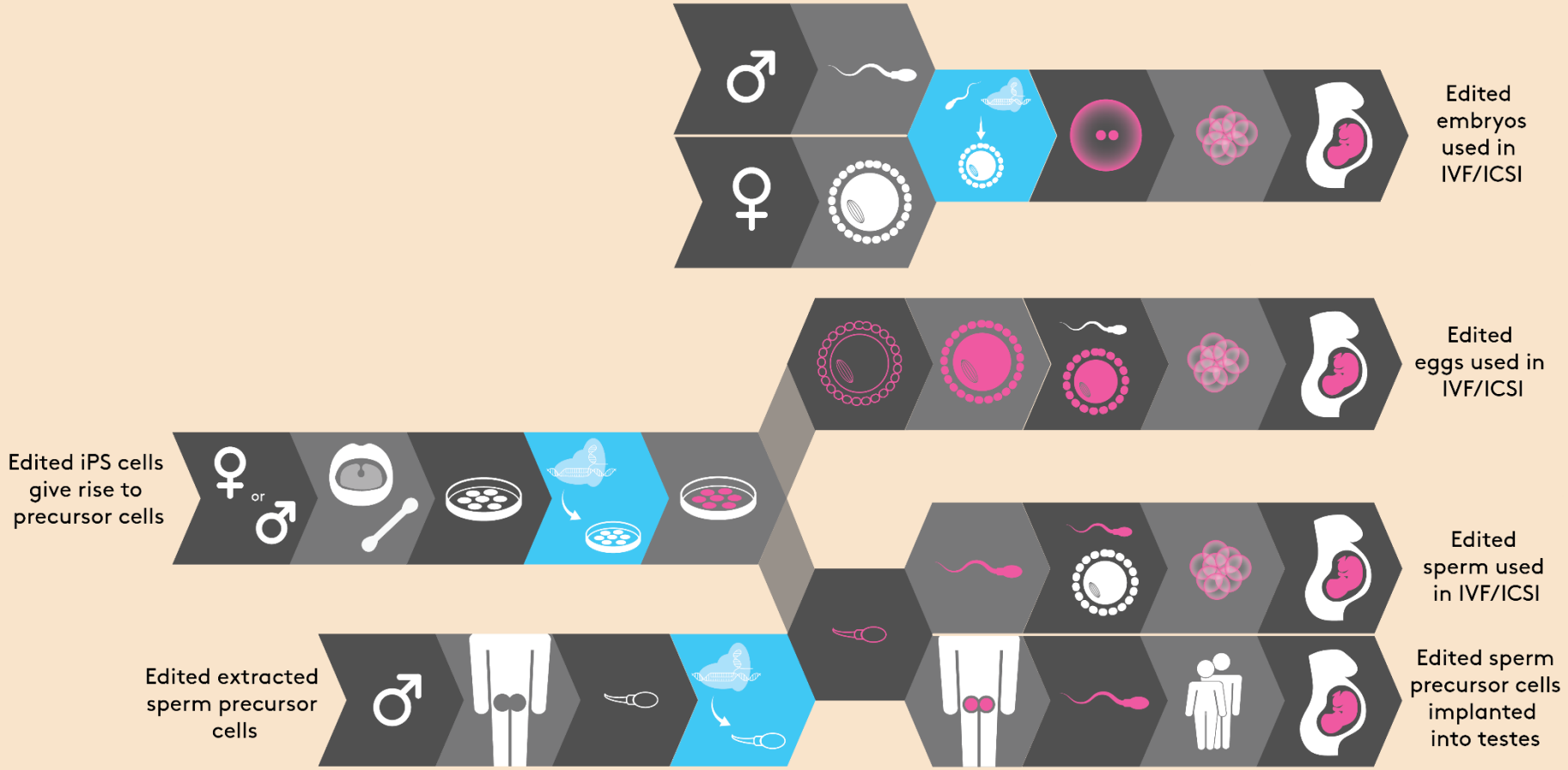
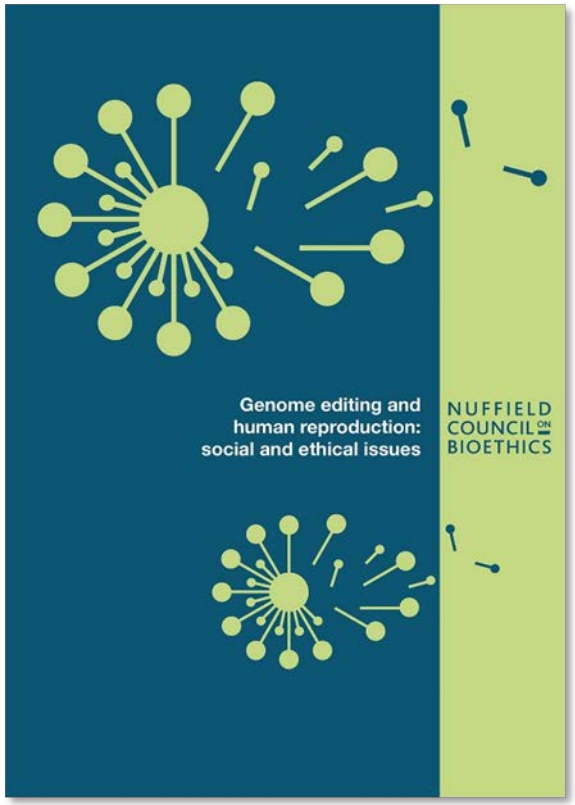
Strategies for genome editing in human reproduction





Recommendations for research

Recommendations for research bodies

Recommendation 1	**We recommend that research to establish the clinical safety and feasibility of genome editing should be supported in the public interest in order to inform the development of evidence-based standards for clinical use**
Recommendation 2	**We recommend that social research that would help to understand the welfare implications for people born following heritable genome editing interventions (e.g. involving people born following preimplantation genetic testing) should also be supported in the public interest**

Recommendations for UK Government

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Recommendation 3	**We recommend that, before any move is made to amend UK legislation in order to permit heritable genome editing interventions, there should be sufficient opportunity for a broad and inclusive societal debate**
Recommendation 4	**We recommend that, without awaiting the opportunity for a thoroughgoing review of the framework legislation, the Secretary of State for Health and Social Care should give consideration to bringing within the scope of licensing any heritable genome editing interventions that currently fall outside that scope**
Recommendation 5	**We recommend that heritable genome editing interventions should be permitted only provided that the impact on those whose vulnerability to adverse effects (including stigmatisation and discrimination) might thereby be increased has been assessed and mitigated (and, in any case, not without open and inclusive consultation with people in those positions)**
Recommendation 6	**We recommend that heritable genome editing interventions should only be permitted provided that arrangements are in place to monitor the effects on those whose interests may be collaterally affected and on society more generally, and provided that legitimate and effective mechanisms are in place to redress those effects and to revise relevant policy; this should include a clear regulatory measure to trigger a moratorium and a sunset provision, requiring review and an affirmative resolution to permit the practice to continue**
Recommendation 7	**We recommend that consideration should be given to the establishment of a separate body or commission in the UK, independent of Government and independent of existing regulatory agencies, which would have the function of helping to identify and produce an understanding of public interest(s) through promotion of public debate, engagement with publics and monitoring the effects of relevant technological developments on the interests of potentially marginalised subjects and on social norms**

Recommendations for governments in UK and elsewhere

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Recommendation 8	**We recommend that broad and inclusive societal debate about heritable genome editing interventions should be encouraged and supported without delay**
Recommendation 9	**We recommend, in the light of the potential for new forms of discrimination on grounds of genetic variation, that governments in the UK and elsewhere give fresh consideration to how these risks may be best addressed**
Recommendation 10	**We recommend that governments in the UK and elsewhere should monitor and give consideration to the use of intellectual property rights in order to promote the public interest in having safe, effective and ethical heritable genome editing interventions**
Recommendation 11	**We recommend that governments in the UK and elsewhere should work with international human rights institutions such as the Council of Europe and UNESCO to promote international dialogue and governance with regard to heritable genome editing research and innovation**
Recommendation 12	**We recommend that governments in the UK and elsewhere give consideration to bringing forward an international Declaration affirming that people whose genomes have been edited should be entitled to the full enjoyment of human rights**

Recommendations for licensing and regulation

Recommendations regarding licensing and regulation

Recommendation 13	**We recommend that genome editing should be licensed for clinical use only once risks of adverse outcomes have been assessed by a national competent authority (in the UK, the HFEA)**
Recommendation 14	**We recommend that heritable genome editing interventions should initially be licensed on a case-by-case basis**
Recommendation 15	**We recommend that heritable genome editing interventions should be introduced only within the context of well-designed and supervised studies, reporting regularly to a national coordinating authority, and that the effect on individuals and society, including over generations, should be closely monitored as far as possible, compatibly with the privacy of the individuals concerned**

What is at stake for prospective parents?

- They *want to have a child*, and
- they want the child they have to be *genetically related to them* (otherwise the pre-established likelihood of the child having a pre-identified genetic condition disappears or, at least, changes), and
- they want the child they have *not to have a specified condition* that there is a supposed likelihood that that child will have (which means, at the genetic level, they want the child to have one kind of genetic variant rather than another), and/or
- they want the child they have *to have a specified characteristic* that there is a supposed likelihood that that child will *not* have (or, again, they want the child to have one kind of genetic variant rather than another).

i.e. they don't want *these* children they want *those* children – though the motivation may be imponderable the decision about how to achieve that outcome involves deliberate agency.

The epistemic position

As a result of expanding genetic testing, genome sequencing and genomics research there is increasing:

- understanding of the role and functioning of the genome in humans, and
- information about their genotype accessible to individuals

Prospective parents increasingly face reproductive decisions equipped with genetic information that has practical significance in a given context of action

The sociotechnical context

Given access to certain genomic knowledge and genotype information, prospective parents can potentially decide

- to refuse the information (although, in the context in which the information would be available this is, nevertheless, a moral choice) or
- to act on the information; there are many options available, including:
  - not having a child, or
  - having a child who is:
    - not genetically-related, through:
      - adoption, or
      - gamete donation (intra familial, extra familial), or
    - genetically-related, through:
      - selective methods, such as:
        - prenatal (PND/ToP) or
        - preimplantation (PGD), or
      - *editing methods (HDR, base editing, epigenome editing)*

Methods other than genome editing could result in a genetically related child while excluding/including a heritable genetic trait in all but a very small number of cases.

That's not really the point, however...

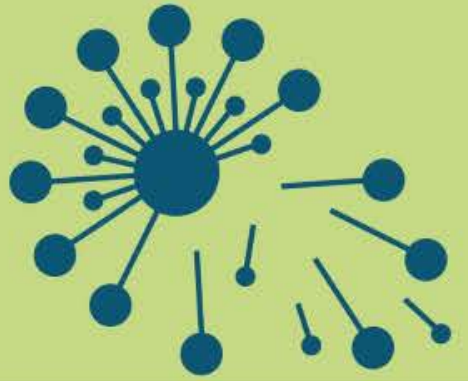
What's new?

People approach reproduction in

- novel *epistemic position* (genomic research, genetic testing)
- novel *technoscientific conditions* (ARTs, reprogenetics, GE?)

Technological perspective

- dynamic relationship between technology and norms
- *what role for moral agency?*
- *what next*?



Context and questions

So, there are two major considerations:

- the epistemic position from which people confront complex reproductive decisions, and
- the sociotechnical context in which they do so, which defines the options they have for exercising their agency.

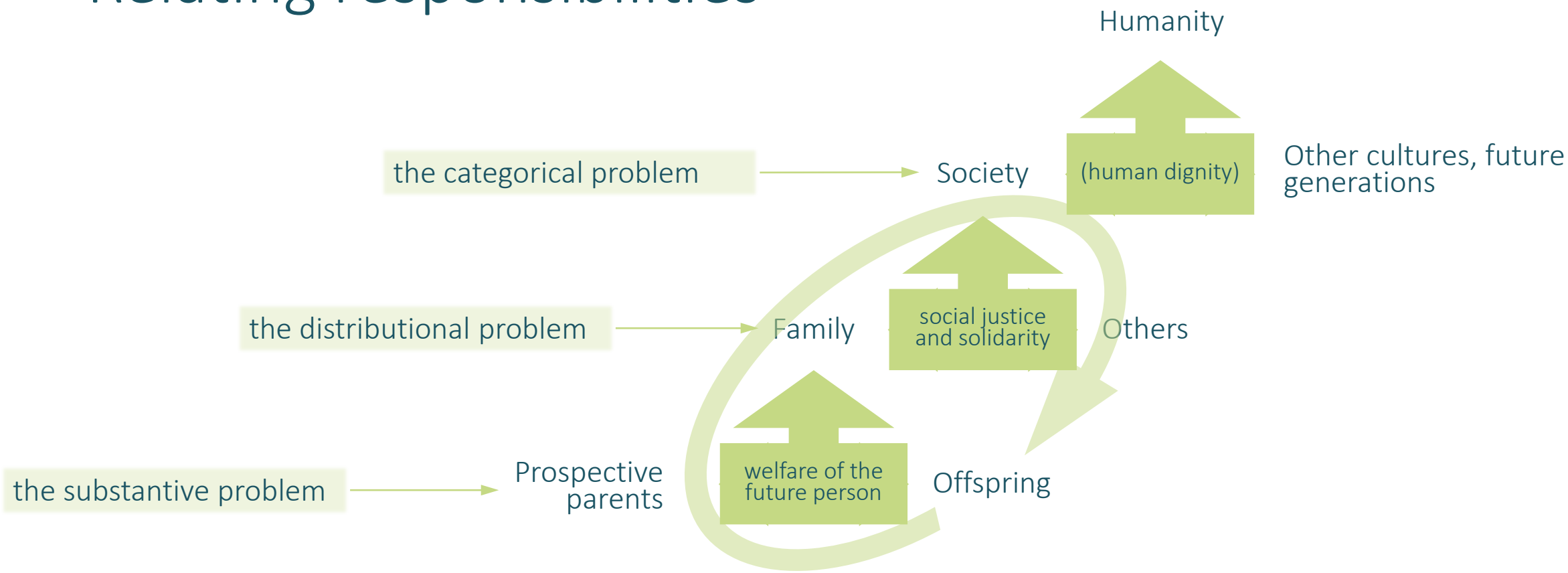
In theory, people are responsible for their *decisions* but…

… society is responsible for their *options*.

The epistemic position (new knowledge) and the sociotechnical context (new powers of agency) create new conditions of *responsibility* for individuals and for society

- How should we think about the relationship between these interests and responsibilities? In what circumstances, in what ways and to what extent should people be permitted, enabled and assisted to pursue their goals?
- If the technology proves safe and effective, what further uses might we find for it? How should we shape the future innovation, diffusion and application of heritable genome editing technologies to secure the sort of society we want?

Relating responsibilities

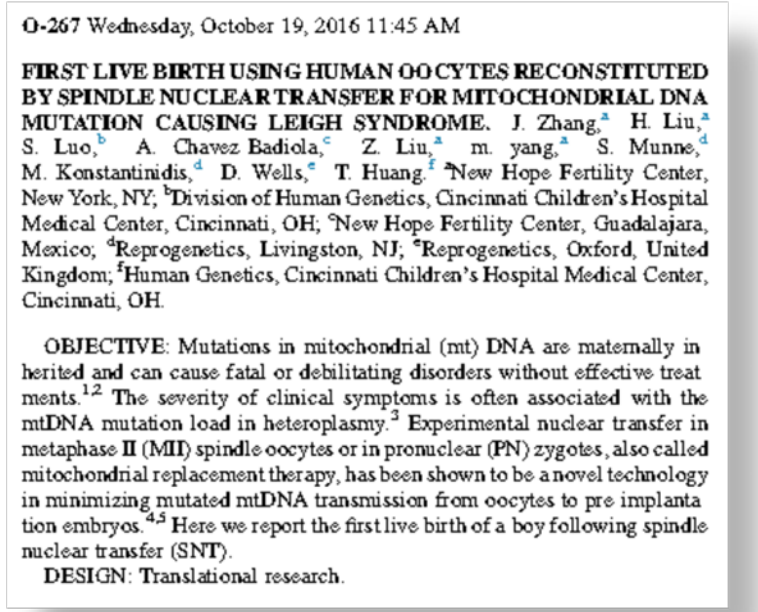


Technology transfer and 'geo-ethics'

- Knowledge, biological samples, technologies, experts and patients are internationally mobile
- Concerns about technology transfer and equity

"In relation to possible applications, of most concern is the potential for treatments based on gene editing techniques to be offered prematurely and to find ready customers on the international health market, ahead of adequate tests to determine safety and efficacy."

Chan S and Medina Arellano M (2016) Genome editing and international regulatory challenges: Lessons from Mexico, *Ethics, Medicine and Public Health* **2**(3): 426-434



O-267 Wednesday, October 19, 2016 11:45 AM

FIRST LIVE BIRTH USING HUMAN OOCYTES RECONSTITUTED BY SPINDLE NUCLEAR TRANSFER FOR MITOCHONDRIAL DNA MUTATION CAUSING LEIGH SYNDROME. J. Zhang,[a] H. Liu,[a] S. Luo,[b] A. Chavez Badiola,[c] Z. Liu,[a] m. yang,[a] S. Munne,[d] M. Konstantinidis,[d] D. Wells,[e] T. Huang.[f] [a]New Hope Fertility Center, New York, NY; [b]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [c]New Hope Fertility Center, Guadalajara, Mexico; [d]Reprogenetics, Livingston, NJ; [e]Reprogenetics, Oxford, United Kingdom; [f]Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

OBJECTIVE: Mutations in mitochondrial (mt) DNA are maternally inherited and can cause fatal or debilitating disorders without effective treatments.[1,2] The severity of clinical symptoms is often associated with the mtDNA mutation load in heteroplasmy.[3] Experimental nuclear transfer in metaphase II (MII) spindle oocytes or in pronuclear (PN) zygotes, also called mitochondrial replacement therapy, has been shown to be a novel technology in minimizing mutated mtDNA transmission from oocytes to pre implantation embryos.[4,5] Here we report the first live birth of a boy following spindle nuclear transfer (SNT).

DESIGN: Translational research.

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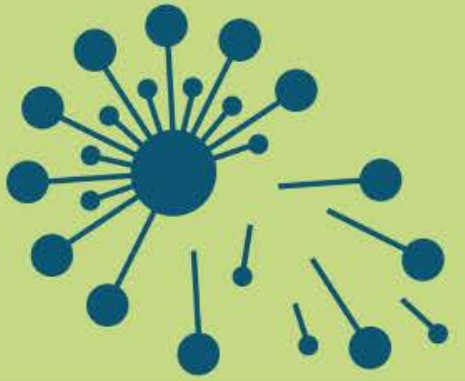
Map image from: Araki M and Ishii T (2014) International regulatory landscape and integration of corrective genome editing into in vitro fertilization, *Reproductive Biology and Endocrinology* **12**:108

see also: Palacios-González C and Medina-Arellano M (2017) Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case, *Journal of Law and the Biosciences* **4**(1): 50–69

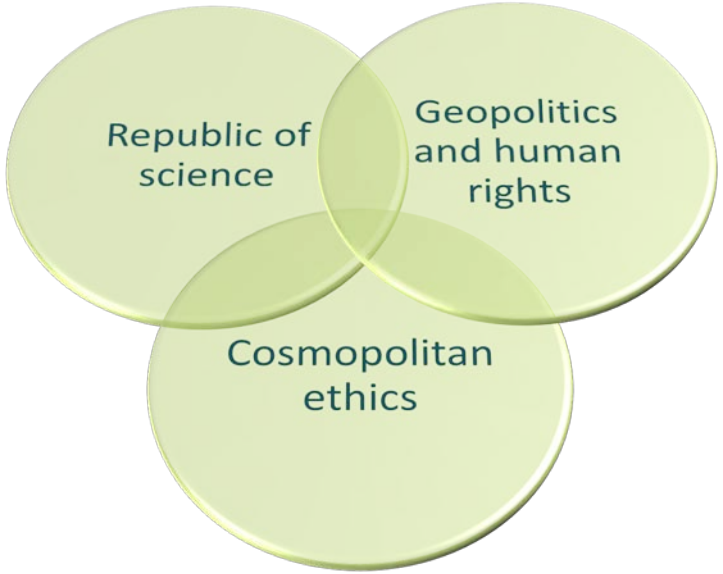


The need for a 'geo-ethics'

4.31 As practices move between jurisdictions across ethical thresholds, one likely consequence is a form of 'ethical arbitrage' that may have the effect of eroding these differences.[407] This is a matter of concern in relation to technology transfer, particularly across pronounced socio-economic gradients (e.g. between the global north and the global south). In such cases, the introduction of technology can act as a Trojan horse, introducing other forms of dependency on foreign expertise, products and investment and providing a vector for cultural and ethical values, one that potentially contributes further to the diffusion and entrenchment of neoliberalism and market economics. Nation states compete or cooperate with each other ultimately to capture economic benefit and geopolitical power. 'Technonationalism' refers to the hoarding and exploitation of technological advantage by nation states, an outcome that can be supported by a variety of measures including tax incentives, access to markets, patent protections, infrastructure (biotech clusters), exploitability of the research base, amenability of the local language and the adoption of common markets and rules concerning the quality and safety of products placed on those markets.[408]

4.33 Globalisation has recently provoked a backlash, an overreaction every bit as menacing to cosmopolitan ideals of social justice as neoliberal capitalism.[411] Populism and its reassertion of local cultural values may provide a bulwark against the erosion of ethical borders that has accompanied globalisation. But inasmuch as populism places value on identity and sovereignty, and the biopolitics of populism involves the reassertion of political control over what sort of people may *come into* a jurisdiction, it may also seek to exert political control over what sort of people should come *into being* in a jurisdiction.[412] It is not hard to imagine (given the availability of historical examples from the twentieth century) what the progeny of ethno-nationalism and technonationalism could look like.

Three venues of international discourse



The third venue includes those who are attended to but not reflected in the republic of science, and incorporated but not represented/expressed in the political discourse.

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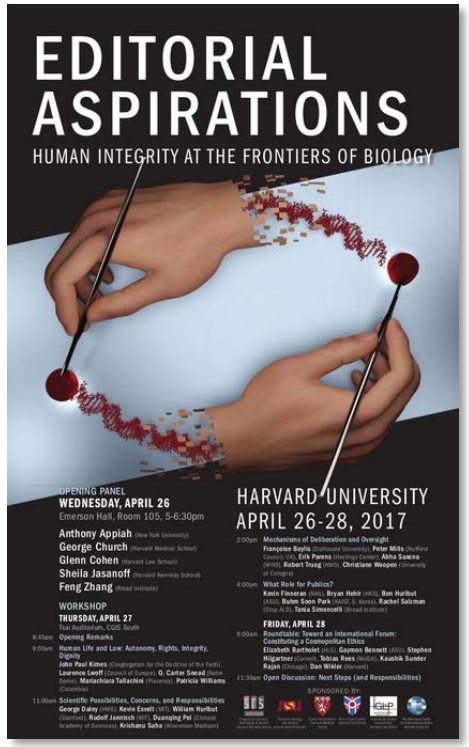
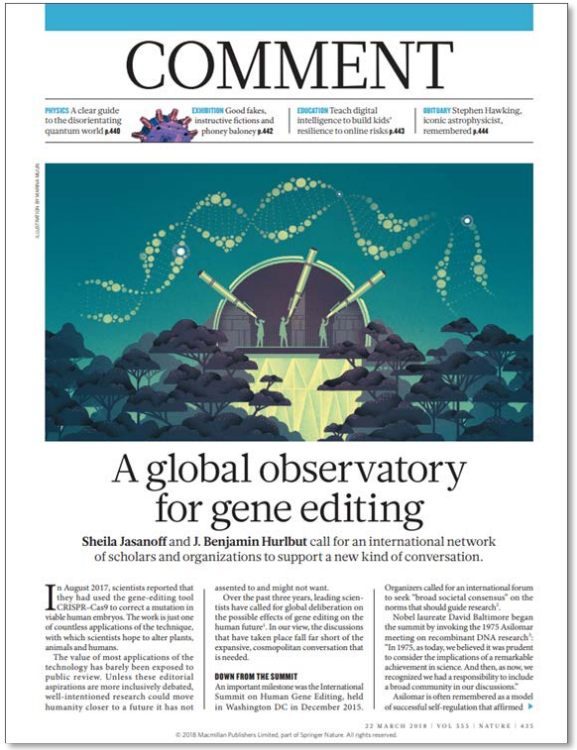
A global observatory for genome editing




COMMENT

PHYSICS A clear guide to the disorientating quantum world p.440 | EXHIBITION Good fakes, instructive fictions and phoney baloney p.442 | EDUCATION Teach digital intelligence to build kids' resilience to online risks p.443 | OBITUARY Stephen Hawking, iconic astrophysicist, remembered p.444

A global observatory for gene editing

Sheila Jasanoff and **J. Benjamin Hurlbut** call for an international network of scholars and organizations to support a new kind of conversation.


Trends in Biotechnology

CellPress REVIEWS

Scientific Life

Building Capacity for a Global Genome Editing Observatory: Conceptual Challenges


Trends in Biotechnology

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Building Capacity for a Global Genome Editing Observatory: Institutional Design