Genome editing and bioethics

Thinking about applications in human reproduction

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The Nuffield Council on Bioethics

- Established in 1991
- Funded by the Nuffield Foundation, Wellcome Trust & Medical Research Council

Terms of reference:

- To identify and define ethical questions raised by recent advances in biological and medical research in order to respond to and anticipate public concern
- To examine and report on such questions with a view to promoting public understanding and discussion
- In the light of the outcome of its work, to publish reports; and to make representations

UK context: law and regulation

- All use of gametes and embryos in vitro prohibited unless licenced and overseen by the regulator - Human Fertilisation and Embryology Authority (HFEA)
- Licences for **research**: HFE Act specifies *purpose* of research rather than the procedure or tools used*:* can authorise research that is 'necessary or desirable' using gametes or embryos from IVF surplus or created for research
- Licences for **treatment**: HFE Act specifies what is a 'permitted' gamete or embryo – one "whose nuclear or mitochondrial DNA has not been altered"

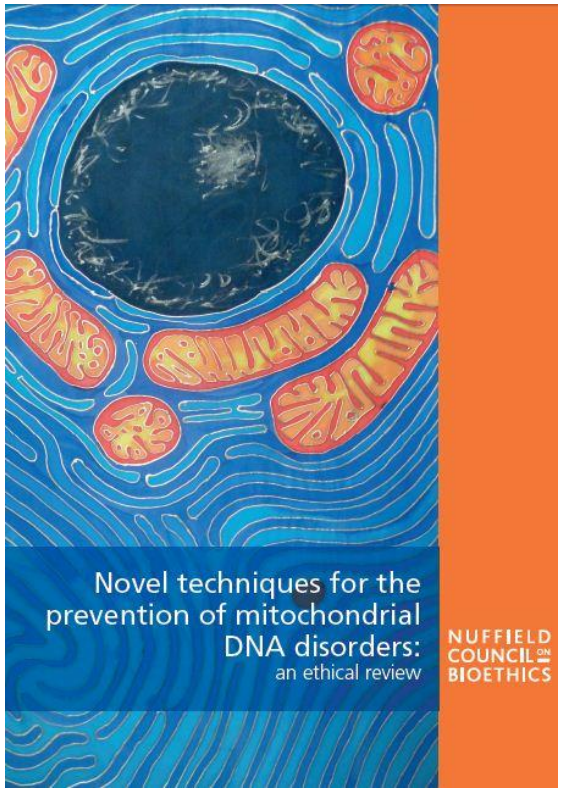
Exception: mitochondrial disorders

- 2015: Regulations made to permit use of reconstructed embryos in treatment for the *purpose* of avoiding transmission of mitochondrial disorders
- No stated intention of opening up legislation for other purposes – government position: *"the use of genetically modified sperm, eggs or embryos in treatment is illegal"*

In 2012 we concluded…

*"The novel treatments under discussion were viewed by the Working Group as examples of **germline therapies**.*

"The wider policy debate could benefit from a fuller discussion of the ethics of the different kinds of prospective and theoretical germline therapies than was possible within the remit of this report. This would include potential therapies that would act on the cell nucleus with heritable effects, and therapies which might involve nuclear transfer in its various forms."



Genome editing: a transformative technology?

- **Flexible** (can be used for DNA/ RNA molecules)
- **Effective** (at making targeted alterations without off-target effects)
- **Relatively rapid** (research time reduced from years to months)
- **Relatively accessible** (can be used by adept microbiologists)
- **Relatively cheap** (compared to alternatives)
- …and continually **developing**

So: increasing rate and diffusion of use

But: limitations in delivery, genetic knowledge, phenotype, etc

A two-stage programme of work

- Stage 1 – review of conceptual and descriptive issues, leading to identification and prioritisation of key ethical questions (beginning with the technology and examining its potential applications)
- Stage 2 – examination of normative questions leading to practical recommendations in a defined area of activity (beginning with challenges and looking at the impact of technology in meeting – and transforming – those challenges)

Method of working (stage one)

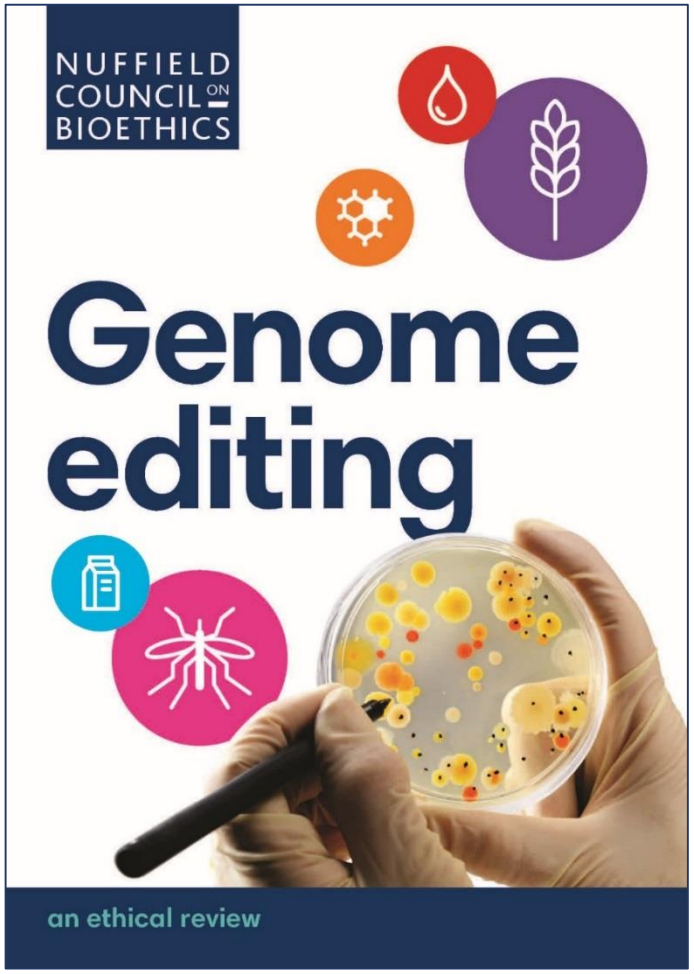
- Commissioned background paper
- Workshops
- Interdisciplinary working group
- Open call for evidence
- Literature review
- ‘Fact-finding’ meetings
- Research interviews
- External review

Genome editing: an ethical review

Published September 2016

a review of conceptual and descriptive issues

→identification and prioritisation of key ethical *questions*



Public interest

- Expectation of future **benefits**
- Possible **costs** and **harms**
- **Investments** – money and trust
- Moral and cultural **values** and **understandings**

Moral perspectives

Social justice..

special consideration may be appropriate regarding possible negative effects that could cause discrimination, injustice or disadvantage

Science as a moral enterprise..

centres on the idea that the pursuit of scientific knowledge should benefit society

Welfare & risk..

suggests potentially measurable consequences by which to judge genome editing e.g. expected benefits and possible harms

Governance & democracy..

democratic procedures that take into account the range of views people have will be important in developing regulatory and practical ways forward

Intervening in the genome..

is significant and distinctive due to the role of the genome in determining biological features and inheritance

Human rights..

concerns that a technology may infringe human rights may offer grounds for justifying **or** resisting interference by the state or others

Moral conservatism..

reflects concerns about the motives of deliberate human intervention in complex biological processes

Next phase

Taking on the *challenges*: examining ethical questions and practical ways forward in two areas of application identified as high priority:

- Human reproduction (publishing in 2018)
- Livestock (publishing in 2019)

Other issues identified

Issues that may need to be addressed in the near future

- Use of CRISPR-Cas9-enabled gene drive systems in wild species to prevent infectious disease transmission
- Use of genome editing to make animal tissues and cells suitable for xenotransplantation

Issues that should be kept under review

- Genome editing to develop new cell-based therapies for existing diseases
- Use of genome editing to develop new plant strains in agriculture
- Changing patterns of technology use, including military and national security initiatives, artistic and cultural activities, and private experiments by community groups or individuals

Human genome editing in UK research

- First and only licence for genome editing in human embryos granted to the Niakan laboratory, the Frances Crick Institute in February 2016 to use genome editing in basic research to understand the early development of embryos.
- Currently no intended clinical or reproductive applications (which would require legislative change)

Human genome editing – our aims

- To **examine ethical questions** relating to the attempted influence of inherited characteristics in humans, in the light of the likely impact of genome editing technologies.
- To **review relevant institutional, national and international policies and provisions**, and to assess their suitability in the light of the ethical questions examined.
- To report on these matters and to **make recommendations** relating to policy and practice

Key ethical concerns

- Risks of **unintended effects** due to off-target DNA alterations
- Implications of genome editing in **reproductive treatment**, for example, making changes that will be passed on to future generations. Issues including outcomes, risks, costs and societal impact have implications for governance and regulation
- Widespread of genome editing may amount to '**liberal' eugenics** driven primarily by the choices of parents
- Potential **benefits and harms** of genome editing might not be **distributed equitably**
- How to delineate **morally acceptable and unacceptable uses** of genome editing for governance purposes
- **Transnational issues -** international regulations and responsibilities

Some problematic distinctions

- **Research versus clinical uses**
- **Health versus disease**
- In some sense all of us are actually or virtually affected by disease, now or in the future
- **Therapy versus enhancement**
- Avoiding the inheritance of single gene conditions v. introducing gene variants that confer ‘desirable’ phenotypic traits
- **Somatic v germline interventions**
- Cell-based therapies (e.g. treating HIV or leukaemia using genome-edited white blood cells)

‘Start from reality’

- Understanding the technical potential and limitations of genome editing
- Identifying the most likely near-term applications
- Understand the context of social and political realities

Human Rights and Reproduction

- The 2018 Report will adopt a broadly *human rights* approach; and
- Argues that we should consider genomic editing within the context of *reproductive choice* and not that of clinical medical treatment

Ethical consideration of genome editing: three sets of considerations

Individuals directly affected: those making reproductive choices and the future child's welfare

Others within society: issues of the public interest and of justice

Future generations: the human genome and human identity

Genome editing and public engagement

> In the UK at least, scientific, ethical, and regulatory agencies have a key role to play. Stellar genomic research institutions such as the Francis Crick Institute should lead and monitor research progress; the Nuffield Council on Bioethics will guide the crucial ethical discussions that need to form the basis of effective public engagement. Work here is already underway, with a framework document on the ethics of genome editing published last autumn and a new report focusing on governance and practice of genome editing expected early next year. The HFEA will need to ensure that the clinical use of genome editing, if it becomes legal, is scrupulously implemented and controlled.

THE LANCET Editorial

Genome editing: science, ethics, and public engagement

Over the past 5 years, genome editing has been rapidly emerging in the biological sciences. In 2015, the American Association for the Advancement of Science chose the genome editing technique known as clustered regularly interspaced short palindromic repeats (CRISPR) as the most promising scientific advancement that year. CRISPR are short sequences that can be used as templates by the CRISPR-associated protein 9 (Cas9) or similar exogenous nucleases. When delivered to a cell, the CRISPR-Cas9 system can cut the genome to excise DNA sequences or introduce new ones.

Using genome editing techniques in germline cells has been controversial, with preliminary research from China using CRISPR-Cas9 in human embryos yielding modest results. But a promising new development became international news with publication, on Aug 2, of new research from a joint US and Korean team reporting findings in *Nature* of CRISPR-Cas9 genome editing of human embryos, targeting mutations in the *MYBPC3* gene that are implicated in hypertrophic cardiomyopathy. Most striking were the team's results when CRISPR-Cas9 genome editing was used in heterozygous zygotes that carried a paternally derived pathogenic *MYBPC3* mutation; 72% of embryos later assessed were free of the pathogenic *MYBPC3* mutation, with no off-target effects and minimal mosaicism. Surprisingly, DNA repair after editing of the mutated allele defaulted to using the maternal allele as a template for DNA repair, rather than the exogenous synthetic single-stranded DNA template.

What do these results mean, not only for ongoing and future research into genome editing of embryos, but also for the potential of clinical application and the myriad of ethical and legal challenges that lie ahead? One certainty is that replication and improvement of the latest research will need to be demonstrated in thousands of human embryos before clinical use can be contemplated, which will take many years to achieve. Understanding why DNA repair during editing of the paternal pathogenic mutation reverted to the maternal wild-type allele suggests a different DNA repair mechanism for zygotes, which will be an immediate research priority.

An obvious starting point for ethical consideration is to address the value of genome editing in embryos, given that pre-implantation genetic diagnosis (PGD) is available in many countries. Genome editing of embryos could complement, or be an alternative to, PGD, especially if fertility is compromised in the case of inherited genetic mutations such as those in *BRCA1*. Conversely, genome editing of human embryos may be viewed as a more ethical approach than PGD, with its aim of embryo repair, rather than destruction.

Public engagement with ethical deliberations will be critical, and needs to happen in parallel with scientific development. No matter how rapid ongoing and future genome editing may be in confirming and improving the results of the latest research findings, the path towards clinical use of genome editing in embryos will ultimately require legal change. The case of clinical uptake of mitochondrial transfer in the UK, for example, is instructive and sobering. It took over a decade from having research licensed by the Human Fertilisation and Embryology Authority (HFEA) to clinical application of mitochondrial transfer techniques, and without the need for new primary legislation. Any future approval for the clinical use of genome editing in embryos—more controversial than mitochondrial transfer—will require new legislation, and will only be politically viable if both scientific advancement and public engagement of the ethical considerations have been exhaustive and effective.

In the UK at least, scientific, ethical, and regulatory agencies have a key role to play. Stellar genomic research institutions such as the Francis Crick Institute should lead and monitor research progress; the Nuffield Council on Bioethics will guide the crucial ethical discussions that need to form the basis of effective public engagement. Work here is already underway, with a framework document on the ethics of genome editing published last autumn and a new report focusing on governance and practice of genome editing expected early next year. The HFEA will need to ensure that the clinical use of genome editing, if it becomes legal, is scrupulously implemented and controlled.

Perhaps the overarching message from the fast-evolving work of human genome editing lies in the importance of engagement: the interdependence of science, ethics, and public consultation. If this is done well, the best possible environment can be fostered to enable progress in the informed decision-making that will be required to help contribute to a profoundly ethical objective: the prevention of heritable genetic diseases. ■ *The Lancet*

For the *Nature* publication see http://www.nature.com/nature/journal/vaop/ncurrent/full/nature23305.html

For the Nuffield Council on Bioethics report see http://nuffieldbioethics.org/project/genome-editing/ethical-review-published-september-2016

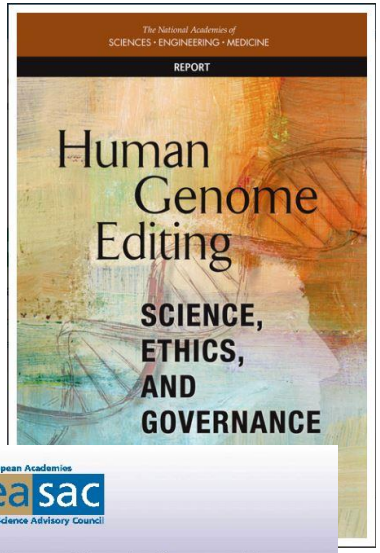
Recent UK initiatives

- **Parliament:** House of Commons select committee on science and technology Genomics and Genome Editing inquiry (November 2016 - ?)
- **Academia:** Cambridge Stem Cells and Public Policy Strategic Research initiatives workshop (January 2016)
- **Learned societies:** Royal Society scoping work on genome technologies, Royal Society of Medicine event in February 2017
- **Patient organisations:** Genetic Alliance UK report (November 2016)

Major international work

- US NAS/NAM report (February 2017)
- European Academies Science Advisory Council (EASAC) report (March 2017)
- Deutscher Ethikrat, as doc recommendation (2017)
- Health Council of the Netherlands (2017)

Acknowledging public concern and need for public engagement strategies



Governance of therapeutic genomic editing for the U.K.

- National governance within a global context: mobility of persons and research; international and trans-national rules and institutions
- Regulation by the HFEA as an ALB (Arms Length Body)
- Licensing of centre/clinic and then of applications to treat
- PGD (by condition); Mitochondrial replacement (by individual)
- Statutory test: risk of inheriting a condition that exposes person to significant risk of a serious condition
- Amendment of HFE Act

But before that….

- **Securing legislative change:**
  - Identifying the critical issues
  - Engaging in extensive public consultation (both to inform and to gauge views)
  - Reviewing relevant submissions (including Nuffield reports)
  - Recommendations to Government

Stay tuned…

www.nuffieldbioethics.org/project/genome-editing

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