Genome Editing and Human Reproduction: Social and Ethical Issues

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The Policy

Synopsis
CRISPR-Cas9 — a gene editing technology — and recent work on alterations to human embryonic genomes in China have shone a new light on the rapidly advancing realm of genomic editing in the world today, highlighting its potential impacts on human health, reproductive futures, and the social fabric of our society. Genome editing and human reproduction: social and ethical issues, a July 2018 report from the Nuffield Council on Bioethics, consists of a timely and careful analysis of bioethical issues directly related to heritable genome editing, including the inevitable societal impacts of such technology. This
The report was compiled by the Nuffield Council on Bioethics, a group of researchers and bioethicists focusing on bioethical issues in the United Kingdom (UK). This report focuses on aspects of the ethics and issues related to specifically heritable genome editing — editing done in germ cells that can be passed on to future offspring.

The first chapter discusses the current landscape and state of genome editing in the world, with a specific emphasis on the UK. This section details (i) the current scientific knowledge of the human genome; (ii) ways that individuals can access clinical genomic testing, if they so desire; (iii) types of genetic editing that are available; and (iv) the responsibilities of individuals and societies to balance the interests of individuals and families with the stakes of genetic editing-related effects on social dynamics and human reproduction. The report states that genomic information is a new layer of knowledge that inherently necessitates a greater level of responsibility for the informed party as to how that information will be used — whether to act on the information and understanding of how that information can affect their understanding of their existence, of humanity, and of relationships with other people. In addition, the report details how the use of heritable genome editing is a complex decision that considers the interests of parents and offspring in selectively editing a genome and the role of societies in blocking or supporting those interests.

The second chapter discusses the current status of genome editing technology and the implications for ethics, science, and social policy. Although the authors acknowledge that it is impossible to predict subsequent developments, this chapter also analyzes how these technologies might advance and evolve in the future by presenting possible case scenarios. Some of the methods of genome editing envisioned include the modification of egg or sperm cells prior to in vitro fertilization, modifying sperm cells and implanting into adult testes, or modification of embryos to be used in in vitro fertilization. The report emphasizes that these editing technologies must be closely compared to other reproductive options to see if there are other options that may be more attractive and technologically more feasible (i.e., using donor gametes), or that leave the technology redundant (i.e., post-partum somatic gene therapy). In addition, the report discusses within this chapter the different reasons why genome editing technology may enter our society; health conditions that are candidates for “treatment” include those that are based in Y chromosome defects, dominant genetic conditions such as Huntington's disease, inversions and deletions in chromosomes, and recessive genetic conditions with two homozygous parents. Finally, the report establishes their perspective that society should focus its consideration on the idea of a future in which genome editing technologies are available (consideration as a “prospective technology”) rather than considering the specific reasons to develop genome technologies. To this end, the report also touches on possible human benefits of heritable genome editing (e.g., stronger immune systems, resistance to environmental changes, super abilities). The report goes on to detail how basic and applied research and public policy must work to support genome editing research and ensure societal benefit from such research.

The third chapter of this report presents essential ethical considerations regarding the potential uses of heritable genomic editing, including concerns of and for the individuals using genomic editing, our society, and humanity. Within this chapter, two principles are presented: first, genetic editing should be carried out with respect and caution for the embryo whose genome is being edited, so that their welfare throughout
their human life is ensured; second, edited embryos should be used only with the assurance that their existence will not worsen social divisions or further marginalize groups in society. The first principle is a responsibility to both science and the embryo’s parents to rigorously evaluate the technical safety of the genome editing technologies. The second principle emphasizes that genome editing should not be used for eugenics [20] — reducing the populations of ethnic minorities or certain sexes. The report goes on to discuss the issues relating to shifting societal norms of reproduction due to the possibility of genome editing — that it may change people’s perspectives on desired characteristics, that some people may benefit more than others, and the impacts of the technology not being accessible to everyone in society. Therefore, the report states that a broad societal debate on the technology that includes individuals who have unequal or increased vulnerabilities due to the usage of the technology (such as disabled individuals and minorities).

The fourth chapter of this report discusses the aspects of governance of genome editing in society through a lens of international legislation, with special focus given to specific pieces of legislation that certain countries and regions (the UK, China, USA, and Europe) have in place to regulate genome editing. This section of the report considers the prospect of individual countries adopting different regulations that reflect different ethical values in a highly interconnected, globalized world. This section provides both concrete recommendations to the UK government on research freedoms, human rights, and alterations to laws and rules, and guidance essential for public input on decision-making concerning genome editing. The report charges the UK government to promptly hold a comprehensive and inclusive public debate about heritable genome editing that evaluates the broad societal challenges of this technology run by a specific separate body or commission independent of the government. The report recommends that the UK government support research in the clinical efficacy and safety of genome editing for clinical usage and social research in the welfare impact of genome editing on individuals born using preimplantation genome editing. The report also recommends that heritable genome editing be initially only approved on a case-by-case basis, and then introduced and used only within strictly designed and controlled studies that have regular reporting requirements to a national coordinating authority (such as the Human Fertilization & Embryology Authority (HFEA) [21] in the UK) and monitor the effects of the technology on individuals and society over many generations.

Finally, chapter five of the report provides the main overall conclusions and recommendations from the working party on the ethical questions, usage of, and regulatory approaches to genomic editing in the present and future. The report concluded that heritable genome editing should continue to be researched, and that it is likely that various CRISPR-Cas9 technologies will be clinically safe and widely available in the future. The report overall provides these main recommendations for future decisions regarding and regulation of genome editing:

- Availability of genetic counseling, strong public education, and access to honest information on genomic editing must increase in both prevalence and accessibility to the public with an increase in the use of genome editing;
- Heritable genome editing should be allowed, enabled, and assisted in certain circumstances, but only with the certainty of two principles: (1) gene editing of gametes or embryos should only be used for the well-being of the future human with an assurance to their overall welfare, and (2) gene editing of gametes or embryos should only be allowed if and only if their existence will not exacerbate social divisions or increase marginalization of groups
within society;
- Heritable genome editing should be introduced to the public only after a broad and in-depth societal debate on the ethical questions pertaining to genome editing; and
- For research bodies, it is important to research both the clinical safety of genomic editing and implications of individuals born with edited genomes, including to understand their welfare.

Context

**Genome editing** [9] — the editing of the genetic information that produces every living thing — is a scientific technology that has rapidly developed in the last few decades [22]. These developments mean that this technology could become broadly accessible in the near future, allowing large groups of people to purposefully alter human genomes. Technologies such as the **CRISPR-Cas9 editing system** [23] allow for the accurate and precise ability to edit genes across the genome that influence different aspects of human development. Using these technologies, **heritable genome editing** [24] could be done to alter genes in gametes and embryos that would thereby be inherited by future offspring. Germline (non-somatic) heritable genome editing lies in contrast to **non-germline (somatic) gene editing** [25], which alters genes in the body's non-reproductive cells and provides therapeutic benefit only to the individual whose genome is edited – not any offspring.

The potential of human genome editing has increased extensively in both ability and prominence with time. The foundations of editing DNA began in the 1970's with the establishment of **DNA sequencing** [26]; advances since that time include the usage of restriction enzymes for **recombinant DNA** [27], the discovery of CRISPR and other technologies to accelerate the ability to edit DNA, and the completion of the internationally backed **Human Genome Project** [28]. Researchers across the world continue to make strides in heritable genome editing, including by determining ways to improve its accuracy, refining and expanding usage of **CRISPR-Cas9** [29], and determining the ethical bounds of using such technologies. In 2015 [30], and reiterated in 2018 [31], the United States **National Institutes of Health (NIH)** [32] expressed a lack of support for the use of gene-editing technologies in human embryos, including a strict restriction on funding research that involves germline gene editing. However, the NIH will **fund research** [33] utilizing CRISPR-Cas9 as a tool in **non-germline (i.e., somatic) gene editing** [34], including to develop patient-specific gene therapies. In 2016, research involving human embryonic gene editing was **approved** [35] in Sweden, China, and the United Kingdom.

In the UK and other countries, **preimplantation genetic diagnosis** [36] (PGD) for **in-vitro** fertilized (IVF) embryos is currently **available** [37] to families at risk of passing on certain serious genetic conditions. **Prenatal diagnosis (PND)** [38], using placenta and amniotic fluid, and **non-invasive prenatal testing or diagnosis (NIPT or NIPD)** [39], using the mother’s blood, is also offered for parents to determine if their fetus has inherited a genetic condition. Genetic disorders can often cause great **physical, psychological, and social challenges** [40] for those who are afflicted with them, including a potentially significant reduction to an individual's lifespan. In addition, most of these conditions are heritable through normal modes of reproduction, causing additional concern to families affected with the diseases. There have also been highly publicized and discouraged usages of CRISPR-Cas9 for editing the human genome, namely work by **Dr. Jiankui He** [41] of China, who claims to have edited the genomes of two human embryos to
remove a gene for the proposed aim of protecting them from HIV infection. This monumental claim immediately brought into focus the technological and biological risks still associated with germline genome editing and the multitude of ethical quandaries inherent in germline genome editing — many of which numerous scientists believe He violated.

In response to the rise in genome editing research, there have been several international pushes to regulate research and consider the ethical implications of genome editing. In 2013 the European Union, through their Horizon 2020 research initiative, bolstered its funding for "Responsible Research and Innovation" (RRI) which calls for research scientists to place their research in the context of values and priorities of their societies; this allows burgeoning technologies such as genome editing to be considered in light of the potential contributions to society, safeties and risks of developing them, and the inherent ethical dilemmas associated with its usage. The World Health Organization (WHO) created an advisory committee in December 2018, which is tasked with developing global standards for the governance and regulation of both somatic and germline human gene editing research. Thus far, this group has called for the development of a centralized registry of all human gene editing research. In March 2019, the US National Academy of Sciences, US National Academy of Medicine, and UK Royal Society announced the development of an international commission to determine the scientific and ethical issues surrounding heritable genome editing, then generate standards for permitting clinical trials and heritable genome editing applications. International summits on gene editing have also showcased scientific innovations in genome editing. These summits, including the Second International Summit on Genome Editing held in 2018 in Hong Kong, have held workshops that hold discussions on the ethical and social implications of heritable genome editing and future regulatory needs.

Finally, a notable public discourse has been initiated in the UK concerning public opinion about genome editing. In 2018, the UK Royal Society conducted a survey of over 2,000 people in the UK asking their opinions on genome editing. The majority of individuals responded that genome editing to cure otherwise incurable life-threatening diseases would be a positive contribution for society; further, the usage of genome editing to cure otherwise curable life-threatening diseases or non-life threatening diseases was still deemed a positive contribution to society. Heritable genome editing — editing that would be inherited by children — was also considered positive for society. However, genome editing for cosmetic reasons was rated by most individuals in the survey as a negative for society.

Policy History

The Council held meetings to collect facts on reproductive genetics, genomic research, and bioethics from experts in those fields in March and July of 2017. In 2017, the Council hosted panel interviews with other leaders in genomics industries and research. Then, the council delved into research interviews with reproductive and disability rights advocates between May and August 2017. They then launched a public questionnaire on three potential genome editing scenarios for eight weeks in May 2017, with 320 individual responses from members of the public collected and used to help further shape the considerations of the working group. Then, they externally commissioned two evidence reviews. Finally, in April 2018, the Council released a draft of the report for external review to researchers across many
disciplines. Following this review, the Council released the final report in July 2018.

The Science

Learn About the Science

CRISPR-Cas9 and Genome Editing [52]

SEE ALL EXPLAINERS [53]

Science Synopsis

The human genome [54] is the full genetic instruction manual unique to every living being that directs the development, functioning, and regulation of the such entity. The human genome is made up of 22 paired autosomal chromosomes [55] and one pair of sex chromosomes [56] (46 chromosomes total); each human receives one of each chromosome in a pair from either of its genetic parents. Within each chromosome lies two copies of the a gene; genes are made up of DNA [57], the informational blueprint that is used to create all RNA [58] and then ultimately proteins [59], which dictate structure and regulation in the body. The operations of the human genome are also impacted by the epigenome [60] — a system by which chemical compounds influenced by external factors such as environmental stressors and disease that regulate and alter gene expression. The human genome is essential to the development of life and impacts the genome of all progeny; therefore, alterations in genomic composition can have a wide range of effects and implications.

Genetic disorders [61] that originate from abnormalities in the genetic code can occur as a single gene disorder [62] or a polygenic/complex disorder [63], depending on both the number of genes and factors that can be directly tied to influencing a disease state and the number of genes that would have to be edited in order to treat that disorder. These abnormalities can lead to a range of debilitating diseases, such as Duchenne muscular dystrophy [64] (i.e., a disease of muscle degeneration caused by a mutation in the dystrophin gene on the X chromosome) or cystic fibrosis [65] (i.e., a disease causing thick, airway-clogging mucosal secretions caused by a deletion in the cystic fibrosis transmembrane conductance regulator gene). Altering the human genome at the specific sites of the genome is called genome editing [9]. Genome editing can be done via a number of different biological tools for altering the genome, including zinc-finger nucleases (also known as ZFNs [66]), transcription activator-like effector nucleases (also known as TALENs [67]), and CRISPR-Cas9 [68]. Consistent amongst these tools is first, the ability to identify the specific locations in the genome that are intended to be edited, and second, the ability to perform the edit in the genome successfully. As compared to the other tools, CRISPR-Cas9 — the most recent development in gene editing technology — is more efficient, more accurate, and cheaper to use, which had let to its proliferation in genetic research labs as a therapeutic tool to edit genomes for a range of disease-causing mutations.
Genomic editing that targets an individual patient’s cells and alters the genome in those somatic cells is called **somatic genome editing** [69]. In this case, the therapeutic benefit of the gene editing is limited to the individual patient’s body. In contrast, **germline editing** [70] alters the genomes within sperm and egg cells to induce changes that could be passed onto future generations. Both types of genome editing can result in varying levels of effectiveness and also have the potential to produce off-target effects in the genome. Germline editing provides an opportunity to prevent certain genetic-based diseases from being inherited, including Y-chromosome disease, inversions and deletions of chromosome segments, Huntington’s Disease, or recessive genetic conditions. Possibilities for germline genomic editing strategies include (1) editing of genomes in embryos established for eventual **in-vitro fertilization** [14] or **intracytoplasmic sperm injection (ICSI)** [71]; (2) editing the genomes of stem cells that will become edited sperm or egg cells to use in IVF; or (3) **editing extracted sperm cells** [72] that are then reintroduced into the male patient for eventual intercourse-based reproduction (which to date has only been **proven** [73] in rhesus macaques).

Although genome editing holds potential for therapeutic and clinical applications, there are still significant challenges to overcome. These challenges include the difficulty of accurately and precisely altering the genome to treat **single gene disorders** [62] versus **complex disorders** [74] that may encompass the activity of multiple genes, and mitigating the potential for **off-target effects** [75] (areas of unintended alterations in the genome during editing). The report identified three main hurdles for genome editing, including (1) needing technology that can sequence genomes accurately and cheaply, and can handle big data storage; (2) acquiring enough knowledge and information to be effectively able to identify and approach the various genetic factors informing a disease state; and (3) insurance that an alteration in an organism produces a desired effect and no negative “collateral” off-target effects.

### Scientific Assumptions

- **CRISPR-Cas9 will be clinically safe in the foreseeable future (Section 5.5, page 155):** Research on CRISPR-Cas9 has recently extended to therapeutic applications in humans, with the first human trials in the United States using CRISPR as a therapeutic tool being **conducted** [76] in April 2019 [77]. Continued **innovations** [78] in the accuracy and safety of CRISPR are expected to continue in scientific research labs.

- **There will be no technological limit in the future to halt the current trends in genome sequencing of declining cost and increasing speed and completeness (Section 2.25, page 42):** Research supports this assumption; CRISPR-Cas9 has shown a tremendous rapid development in feasibility of use for genome editing, with **research** [79] from 2018 identifying areas of improvement to continue improving the speed and accuracy of the editing technology.

### Relevant Experts

- **Nita Farahany, JD, PhD**
  - **Position:** Director of the Duke Initiative for Science and Society; Faculty Chair of the MA in Bioethics & Science Policy; Professor of Law; Professor of Philosophy
  - **Affiliation:** Duke University
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- **Misha Angrist, PhD**
  - **Position:** Senior Fellow in Science & Society; Associate Professor of the Practice, SSRI; Visiting Associate
The Debate

Scientific Controversies / Uncertainties

The precision of using CRISPR-Cas9 for gene editing is still debated in research. CRISPR-Cas9 is still in development to improve both accuracy [84] and precision in editing; poor accuracy may induce off-target effects [85] in the genome, which could lead to important genes functioning incorrectly or not at all. The consequences of potential mosaicism [86] after genome editing — having a mixture of edited cells and non-edited cells — is also a concern, as researchers do not fully understand possible consequences of having a mixture of such cells.

Many scientists [87] as early as 2015 urged their peers to avoid editing the human germline until engaging in dialogue to determine a set of best practices for ethical application of heritable genome editing. However, there was not a clear consensus among scientists regarding the ethics [88] of potentially conducting heritable genome editing and how to best approach these issues. Points of concern raised included the safety of the editing process, usage of editing for cosmetic changes in future children (i.e., creation of “designer babies” [89] with chosen characteristics), and off-target effects. Conversely, there were researchers who proposed [90] that discussions on heritable genome editing should focus on the potential benefits of the technology, and argued [91] that it was “morally imperative” to continue conducting gene editing research in human embryos to advance human health.

The editing of embryonic human genomes remains a highly contentious topic amongst both the scientific population and the public. In November 2018, Dr. Jiankui He announced his work [92] in China that produced two babies resulting from germline genome editing intended to protect the babies from contracting HIV by introducing a mutation in the CCR5 [93] gene, which codes for a receptor that HIV binds to in order to enter and infect cells. Multiple [94] scientists [95] across the globe as well as government officials in China and the United States immediately decried the usage of gene editing tools in human embryos. In March 2019, a group of eighteen of the world’s most prominent genome editing scientists and bioethicists published a commentary [96] in Nature calling for a moratorium on genome editing in human embryos. Scientists [97] have also pushed for conversations to determine future steps and the governance of this technology, with some arguing against [98] the moratorium on genome editing.
and its potential impact on future human therapies. Additional concerns around the use of heritable genome editing include a potential reduction of the number of individuals born with disabilities and who belong to a disability culture, and the further marginalization of individuals belonging to marginalized backgrounds, including gender, ethnicity, socioeconomic status, and race.

**Endorsements & Opposition**

- Marcy Darnovsky, PhD (Executive Director of the Center for Genetics and Society), *opinion article*, July 17, 2018: “Sadly, the Nuffield Council on Bioethics has given its blessing to an unneeded and societally dangerous biotechnology, one that could be leveraged by privileged elites seeking purported genetic improvements to ensure that their children are treated as superior to the rest of us…[We can] affirm the widespread rejection of heritable genetic modification, and reclaim biotechnology as an instrument for fostering solidarity and serving the common good.”

- Dr. Natalie Kofler (Molecular Biologist and Bioethicist, Founding Director of Editing Nature at Yale University), *editorial*, February 26, 2019: “Editing the genes of embryos could change our species’ evolutionary trajectory. Perhaps one day, the technology will eliminate heritable diseases such as sickle-cell anaemia and cystic fibrosis. But it might also eliminate deafness or even brown eyes. In this quest to improve the human race, the strengths of our diversity could be lost, and the rights of already vulnerable populations could be jeopardized. Decisions about how and whether this technology should be used will require an expanded set of scientific virtues: compassion to ensure its applications are designed to be just, humility to ensure its risks are heeded and altruism to ensure its benefits are equitably distributed.”

- David King, PhD (Director of Human Genetics Alert), *news article*, July 17, 2018: “This is an absolute disgrace. We have had international bans on eugenic genetic engineering for 30 years. But this group of scientists thinks it knows better, even though there is absolutely no medical benefit to this whatever. The Nuffield Council doesn’t even bother to say no to outright designer babies.”

- Professor Fiona Watt (Executive Chair of the Medical Research Council), *news article*, July 17, 2018: “We strongly support the report’s call for a public dialogue on this issue, as well as further research into the ethical and social impacts, to ensure this technology continues to be used only in an ethical and legally rigorous way.”

- Sarah Norcross (Director of the Progress Educational Trust), *news report*, July 17, 2018: “We welcome this report’s conclusion that the clinical use of genome editing to make heritable changes may be ethically acceptable, if certain stipulations are met. We also agree with the report’s call for thoroughgoing public debate about this technology, and with its identification of the HFEA as the best placed competent national body to regulate the future use of genome editing in assisted conception.”

- Beth Thompson, PhD, MBE (Head of UK/EU Policy at Wellcome Trust), *press roundup*, July 17, 2018: “Genome editing has huge potential to improve human health, and having clarity on how it could work – both technically and ethically – is essential if it is to benefit patients in the future. The Nuffield Report takes steps to address important ethical questions, and makes clear that, if certain conditions are met, heritable genome editing could be ethically acceptable. Science can only progress with the confidence of society and we will continue to support research that addresses both the scientific and societal challenges raised by genome editing, and encourage an open and inclusive debate on how it should be used.”

**Potential Impacts**

This highly influential and comprehensive report gives important guidelines and recommendations on how heritable genome editing should be used and potentially regulated in the future, and raises vital ethical questions that must be asked of society before widespread availability of the technology. Multiple articles...
have been published following this report discussing its conclusions, with summaries and perspectives on the report available online.

Status

The report was released by the Nuffield Council on Bioethics in July 2018.

Related Policies

**Human Genome Editing: Science, Ethics, and Governance**

This report provides an overview of the current state of genome editing, potential applications and policy issues, and the scientific, ethical, and social issues such technology entails. This report also provides their own 7 “Principles for the Governance of Human Genome Editing.”

**Second International Summit on Human Genome Editing: Continuing the Global Discussion (NASEM Report)**

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