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Center for Genetics and Society

Testimony regarding "Gene Editing Technology: Innovation and Impact"

From: Marcy Darnovsky, PhD, Executive Director and Katie Hasson, PhD, Program Director
To: U.S. Senate Committee on Health, Education, Labor and Pensions
Re: Full Committee Hearing of November 14, 2017 "Gene Editing Technology: Innovation and Impact"

Mr. Chairman and members of the Committee:

Thank you for holding this hearing to explore the urgently important issues raised by recent developments in human gene editing technology. We appreciate having been included among those your staff consulted in preparation for this discussion.

The Center for Genetics and Society is an independent non-profit public-interest organization working to encourage socially responsible uses and governance of human biotechnologies. We work at state, national, and international levels with scholars, scientists, legal experts and leaders in the fields of human rights; social, racial, reproductive, and economic justice; and the environment.

Introduction

Recent technical developments have brought us to a critically important juncture for careful consideration about the implications of human gene editing. These new genetic modification techniques hold both great promise and great risk. If used responsibly and in accordance with commitments to human rights and social justice, they could lead to advances in biological knowledge and improved health outcomes. If misused, they could threaten the health and autonomy of future generations, exacerbate existing social disparities, and lay the basis for new forms of discrimination and inequality based in a resurgence of eugenic ideologies and practices.

These unacceptable risks can be avoided by differentiating, in public policy and in public understanding, between appropriate and inappropriate uses of human gene editing – that is, by supporting the development of safe, effective, and accessible gene editing-based treatments for existing patients, while eschewing efforts to modify the genes that we pass down to our children and future generations. This

distinction has been established as law in more than 40 nations,[1] as well as in several significant international policy instruments, including the Council of Europe's Convention of Human Rights and Biomedicine (the Oviedo Convention)[2].

In addition, opinion research in the United States shows strong wariness about manipulating the genes and traits of future children and generations. Our observations and direct experience over 16 years at the Center for Genetics and Society make clear that support for a ban on reproductive germline modification extends across the political spectrum.[3]

There is no compelling reason to turn our backs on these widely held views. As we explain below, permitting human germline modification for reproductive purposes is unnecessary for any medical purpose. Yet it would expose future children and generations to significant health risks, and set the stage for unacceptably dangerous social consequences, including the exacerbation of existing discrimination and inequality.

Reproductive germline modification is a matter on which there is little plausible "middle ground." If the door to its use is cracked open, limiting its spread and applications will be extraordinarily difficult.

Prohibition of a technological application, even one as extreme as human germline modification, requires strong justification and widespread support. Along with many others, we believe that reproductive germline modification meets that bar.

Critical distinctions

The terms typically used to describe the very different applications of human gene editing are **somatic modification** (or **gene therapy)**, which seeks to alter the cells of a person with a disease, and **germline modification** (also referred to as germline editing for reproduction, inheritable genetic modification, and similar terms), which involves altering eggs, sperm, or early embryos in ways that alter the DNA, and thus the traits, passed down to resulting children, and to any and all of their future offspring.

While somatic gene therapies seek to treat or cure an existing patient, germline modification for human reproduction creates a new person with a pre-specified genetic makeup. Though germline modification is often represented as a medical treatment, it would not treat or cure disease, but instead would aim to prevent the births of children with particular genetic conditions.

It is important to note that this objective can be accomplished now by safe procedures that do not involve genetic manipulations. In other words, while somatic gene editing offers new approaches to treating a range of diseases, germline modification would offer no advantage over existing technologies for preventing children being born with inherited disease. We further explain this key point below.

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[1] Motoko Araki and Tetsuya Ishii, International regulatory landscape and integration of corrective genome editing into in vitro fertilization, *Reproductive Biology and Endocrinology* (24 November 2014) https://doi.org/10.1186/1477-7827-12-108.
See also *BiopolicyWiki,* Center for Genetics and Society's compilation of human biotechnology policies at http://www.biopolicywiki.org/index.php?title=Inheritable_genetic_modification

[2] https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164

[3] See, for example, Open Letter Calls for Prohibition on Reproductive Human Germline Modification https://www.geneticsandsociety.org/internal-content/open-letter-calls-prohibition-reproductive-human-germline-modification

Another distinction that is frequently made in the conversation about gene editing is between **therapy** and **enhancement.** Unlike the conceptually and technically clear line between somatic and germline interventions, the difference between therapy and enhancement is conceptually blurry – there are many conditions that some consider disease and others consider normal human variation – and would be extremely difficult if not impossible to enforce as policy.

The case against germline editing for human reproduction

The prospect of human germline modification raises a number of profound safety, social, ethical, and policy concerns, which we sketch briefly here.

Tenuous medical justification. Much of the appeal for reproductive germline editing lies in the prospect of reducing the occurrence of serious inherited disease. Yet this scenario is misleading, because those at risk of transmitting an inherited disease to their children can already avoid doing so by using existing safe and widely available procedures. In nearly every case, the embryo screening and selection technique known as pre-implantation genetic diagnosis (PGD) can ensure that children will be unaffected by the inheritable condition in question, and that they are genetically related to both biological parents.[4]

A very small number of couples (roughly estimated by UC Davis School of Medicine professor Paul Knoepfler as perhaps one in a million[5]) would not be able to produce any unaffected embryos, and so would not be able to use PGD. For these couples, donated eggs or sperm would provide children who were unaffected by the condition of concern, though genetically related to only one of them. In considerations of reproductive germline modification, this situation is often offered as the justification for permitting human germline modification. Yet while full genetic relatedness to one's children is a preference with which we may sympathize, it is a social benefit rather than a medical matter, and would have to be assessed against the many risks posed by reproductive germline modification.

Unfortunately, many discussions of reproductive germline editing fail to consider – and often to acknowledge – the existing safe alternatives to it. As an example, a preliminary media analysis of news articles and commentaries about germline editing in the *New York Times, Washington Post,* and *Guardian* found that only 15% even mentioned PGD.[6] This lacuna makes it very difficult to meaningfully evaluate germline editing as a prospective method of human reproduction, and significantly skews understanding of what's at stake in the controversy over it.

PGD is not ethically uncontroversial. It poses the difficult question of what kind of children will be welcomed into the world, and whether setting the bar in a way that drastically reduces or eliminates conditions that are considered disabilities will increase the social stigmatization of people living with those conditions. But germline modification raises that prospect to an even greater degree, and carries additional dire safety and societal risks.

[4] See Eric S. Lander, Brave New Genome? *N Engl J Med*, July 2, 2015; 373:5-8
http://www.nejm.org/doi/full/10.1056/NEJMp1506446
[5] Paul Knoepfler, Countering that Pro-Heritable Human CRISPR WSJ Piece, The Niche, October 22, 2017
https://ipscell.com/2017/10/countering-that-pro-heritable-human-crispr-wsj-piece/
[6] Hasmik Djoulakian, Editorial Precision? Snapshot of CRISPR germline in the news, Biopolitical Times, August 1, 2016
https://www.geneticsandsociety.org/biopolitical-times/editorial-precision-snapshot-crispr-germline-news

Some supporters of germline editing for human reproduction assert that it provides an option for those with moral objections to the selection of embryos that PGD entails. However, germline editing could not assuage those concerns, since preliminary investigations of it have already used hundreds of viable human embryos acquired from fertility clinics, and created hundreds more specifically for research.[7] Further, if germline editing were ever used for human reproduction, PGD would be required in order to confirm that the desired alterations had been successfully achieved.

Concerns about the health and well-being of future children and generations. Germline editing with CRISPR and other techniques has a range of known safety risks – off-target effects, unintended insertions and deletions at the targeted site, and mosaic embryos in which some cells are altered and others are not (a condition that could not be reliably ascertained before edited embryos were used to initiate a pregnancy). It is also noteworthy that many germline editing scenarios would involve altering multiple embryos at the moment they are created in vitro, before it is possible to know whether they have the disease-associated variant. Some unaffected embryos would therefore be subjected to any risks introduced by the genetic manipulations.[8]

No matter how precisely genes are altered in or transferred into embryos or gametes, unpredicted and irreversible effects of the editing procedures could manifest in the course of embryonic and fetal development. Some health problems could emerge after the birth of a resulting child, later in the child's life, or in their future offspring.

Technological innovation in medicine often entails potential dangers for early subjects. But experimentation with human germline modification would depart from generally accepted kinds and circumstances of risk. Its effects would reach to future generations, none of whom would have consented to being the subjects of risky experiments, in circumstances where alternative safer approaches had been available, and in which the sole benefit (of full genetic relationship) was one chosen not by them but by their parents.

Concerns about exacerbating social inequality and discrimination. Even interventions undertaken with therapeutic motivations could all too easily put our society on a road toward widespread germline "enhancement" and novel distortions of our commitments to human rights, social inclusion, and equal opportunity.

Definitions of disease and assessments of seriousness change over time and vary among groups and individuals. What some people label as a disease or disability that should be cured, others consider a valued part of their experience and identity. Many people on the "autism spectrum," Little People, and people with Down syndrome, for example, lead fulfilling lives and have no interest in being "cured."

While there are some cases in which a condition caused by a single mutation leads to great suffering and early death, most cases are much less clear cut. Most genetic variants produce increased risk, not certainty, of developing a condition. Many are associated with conditions that would not develop until

[7] See Hong Ma, Shoukhrat Mitalipov, et al., Correction of a pathogenic gene mutation in human embryos, Nature 548, 413–419 (24 August 2017) https://www.nature.com/articles/nature23305 and Liang, P., Ding, C., Sun, H. et al. Protein Cell (2017) 8: 811. https://doi.org/10.1007/s13238-017-0475-6

[8] See Hong Ma, Shoukhrat Mitalipov, et al., Correction of a pathogenic gene mutation in human embryos, Nature 548, 413–419 (24 August 2017) https://www.nature.com/articles/nature23305 and Paul Knoepfler, Top 7 tech hurdles to human germline CRISPR, *The Niche,* November 6, 2017, https://ipscell.com/2017/11/top-7-tech-hurdles-to-human-germline-crispr/

adulthood. How would we delimit "therapeutic" uses of germline editing in terms of a percentage increase in future disease risk? And at what point would this cross the line to enhancement?

Many advocates of reproductive germline editing already support its use to produce preferred traits that are clearly not therapeutic, including those related to appearance, intelligence, and ability. Because traits like these are often influenced by many genes and by the environment, others conclude that we need not worry about so-called "designer babies." But prominent scientists have already identified a number of traits controlled by single genes, such as extra-strong bones, increased physical endurance, and insensitivity to pain. These could be early targets of germline enhancement.

Further, the genetic alterations would not necessarily have to be successful (or even possible) in order for unscrupulous fertility clinics to offer them to parents eager to provide their children the best possible start in life. And just the perception that these genetically enhanced children were superior to their peers would be enough to exacerbate inequalities, particularly as gene editing technologies would likely be available only to the wealthiest families. The result could be a society divided between genetic "haves" and "have-nots." The eugenic logic behind editing out normal human variation labeled as disability and manipulating genes to enhance individual traits is all too familiar, even if it takes a new individually based, technological form.

Widespread international agreement

It is significant for several reasons that dozens of countries, including nearly every nation with advanced biotechnological capabilities, have adopted laws prohibiting human germline modification for reproduction. First, the fact that this has been the outcome everywhere the question was taken up at a national legislative level reflects a rare convergence of considered conclusion resulting from multiple policy processes across a range of democratic societies. Second, it offers a solid policy framework for international cooperation in avoiding both a "race to the bottom" among nations, and the emergence of a dangerous regime of cross-border "shopping" for unauthorized procedures.

In addition to national laws and regulations, a number of international instruments make strong statements against and/or prohibit human germline modification. Article 13 of the Council of Europe's 1997 Convention on Human Rights and Biomedicine (Oviedo Convention) prohibits interventions "seeking to introduce any modification in the genome of any descendants."[9] The Council of Europe reaffirmed Article 13 in its 2015 Statement on Genomic Editing Technologies in light of new techniques such as CRISPR-Cas-9.[10]

Similarly, Article 24 of UNESCO's 1997 Universal Declaration on the Human Genome and Human Rights[11] asserts that "germ-line interventions" could be "contrary to human dignity." A 2015 UNESCO International Bioethics Committee Report updating its reflection on the human genome and human rights reaffirmed its support for Article 13 of the Oviedo Convention. It also stressed the importance of international cooperation, asserting that states and governments should "renounce the possibility of acting alone in relation to engineering the human genome and accept to cooperate on establishing a shared, global standard for this purpose."[12]

[9] Convention on Human Rights and Biomedicine https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164
[10] Statement on Genome Editing Technologies https://www.coe.int/en/web/bioethics/-/gene-editing
[11] Universal Declaration on the Human Genome and Human Rights http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/
[12] Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights 2 October 2015

The organizing committee of the National Academy of Science's and National Academy of Medicine's 2015 International Summit on Human Gene Editing shared these views. That event, which the US National Academy of Sciences and National Academy of Medicine co-hosted with the Chinese Academy of Sciences and the U.K.'s Royal Society, said in its concluding statement:

> While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare.

US opinions on reproductive germline modification

A broad range of Americans, including people across the political spectrum, agree that human germline editing is a line that should not be crossed. Unlike so many issues our country faces today, this one does not readily fall along partisan lines.

The Center for Genetics and Society has collected a number of US opinion polls on inheritable genetic modification, dating back to the mid 1980s.[13] While the results vary substantially, strong majorities consistently oppose germline applications that are likely understood as enhancements (such as blue eyes or high IQ). Opinion is more evenly divided about uses that are characterized as therapeutic, but we have not located any survey data that measures whether or how attitudes about germline modification shift when respondents are made aware of alternatives like PGD or third-party gametes. A recent poll conducted in 2016 by the Pew Research Center[14] shows that most Americans have now heard about germline editing, and that most are more worried than supportive.

Although media attention to new gene editing tools such as CRISPR-Cas9 has heightened awareness among the US public, detailed consideration of its uses remains mostly limited to expert stakeholders such as scientists, other professionals in the biotechnology and fertility industries, bioethicists, and legal scholars. Among these groups, opinion appears deeply divided. Illustrative of this divergence is a pair of commentaries that appeared in 2015 shortly after the first announced research study that used CRISPR on (non-viable) human embryos. One, published in *Science,* was titled "A prudent path forward for genomic engineering and germline gene modification."[15] The other, published in *Nature,* was headlined "Don't edit the human germ line."[16]

Our work at the Center for Genetics and Society involves scholars in a range of disciplines (including public health, public policy, law, the social sciences, humanities, and life sciences) and public interest advocates in a range of civil society sectors (including disability rights; reproductive health, rights, and

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http://unesdoc.unesco.org/images/0023/002332/233258e.pdf

[13] CGS Summary of Public Opinion Polls https://www.geneticsandsociety.org/internal-content/cgs-summary-public-opinion-polls#igmdata

[14] U.S. public opinion on the future use of gene editing http://www.pewinternet.org/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/

[15] David Baltimore et al., A prudent path forward for genomic engineering and germline gene modification, Science, 03 Apr 2015: Vol. 348, Issue 6230, pp. 36-38 http://science.sciencemag.org/content/348/6230/36

[16] Edward Lanphier et al., Don't edit the human germ line, Nature, 12 March 2015 http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111

justice; racial justice; and environmental protection). We can attest to the strength of concern about the social implications of germline editing in these arenas.

There is one point on which nearly all commentators appear to agree: that the decision about whether to permit germline modification as a method of human reproduction is a hugely consequential one that must be based on social as well as technical considerations, and made with broad public engagement rather than by scientists alone. Unfortunately, the resources and commitment that will be required for meaningful public participation in these deliberations have not yet been mobilized.

Our hope is for a robust consideration that fosters public commitment to both democratic processes and scientific endeavors. Support for appropriate uses of human gene editing – and indeed, public trust in science integrity itself – could all too easily be eroded by irresponsible use of powerful new human biotechnologies.

Is there a tenable "middle ground" position on reproductive germline editing?

While official policy deliberations in dozens of nations over several decades unanimously reached the conclusion that development of human genetic modification should be encouraged for somatic therapies, and prohibited for germline modification, a few non-governmental groups recently have asserted what they represent as a "middle ground" and a cautious limited step.

Perhaps the most influential of these is found in the February 2017 report, *Human Genome Editing: Science, Ethics, and Governance,*[17] authored by a committee of the National Academies of Sciences, Engineering, and Medicine (NASEM). In a dramatic departure from the existing international policy consensus, this report recommends support for reproductive germline modification in certain circumstances, with the possibility of expanding those circumstances (including to enhancement purposes) in the future.

The report, which was covered in daily newspapers as well as in the scientific literature, enumerates a number of criteria that it says should precede any reproductive use of germline editing. However, some of these criteria can already be seen eroding. One example is the recommendation that germline editing be permitted only in the "absence of reasonable alternatives." At the report's official release event, a committee member asserted that this criterion would be satisfied if a couple simply indicated a preference for germline editing over an existing alternative.

Other criteria listed in the NASEM report are also unlikely to hold, including the recommendation that germline editing be permitted only if there are "reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition." Currently most countries, including the United States, have no such oversight mechanisms. The US fertility industry is in fact widely seen as dangerously lacking in regulation and oversight. Further, as noted above, the definition of "serious disease or condition" is subjective and imprecise – one of the reasons that led nations around the world to rely on the distinction between somatic and germline modification as the basis for public policy. The NASEM report itself at one point asserts that "germline genome editing would not be permissible" if it were not possible to meet these criteria.[18]

[17] *Human Genome Editing: Science, Ethics, and Governance* https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

[18] Human Genome Editing: Science, Ethics, and Governance, page 190 https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

The 2017 report is also a step away from the more cautious stance and the commitment to public engagement made by another NASEM committee, the one that organized the 2015 "International Summit on Human Gene Editing."[19] Its concluding statement read in part:

> It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.[20]

The 2015 Summit's concluding statement also called for an "ongoing international forum" about the appropriate uses of human gene editing, and specified that this forum "should be inclusive among nations and engage a wide range of perspectives and expertise – including…members of the general public." Unfortunately, no such forum has been convened or planned. Instead, the 2017 NASEM committee's report substitutes its own judgment about the key question – whether germline editing for human reproduction should go forward – and recommends public participation only in matters such as what types of enhancements should be permitted.

Conclusion

In conclusion, we suggest two questions that we believe go to the heart of why we should forgo germline editing for human reproduction:

> ***Given the availability of safe alternatives to reproductive germline editing, what would justify introducing its significant health, ethical, and social risks?***
>
> ***What forms of public engagement and democratic participation can ensure that everyone who would be affected by germline editing – that is, all of us – are able to consider and come to consensus on its use?***

We have reached a crucial moment in deliberations about human germline editing for reproduction, in which decisions with far-reaching consequences are being made. If these decisions are to be legitimate, they must be grounded in responsible science and in widely shared values. Toward this end, we urgently need broad societal engagement and meaningful democratic discussions of this powerful technology's potential benefits and likely harms. No single group of scientists or enterprises has the moral warrant to work around existing restrictions, or to thrust society into an era in which new forms of inequality and discrimination are attributed to our genes.

In our view, permitting human germline editing for any reason would likely lead to its escape from regulatory limits, to its adoption for enhancement purposes, and to the emergence of a market-based eugenics that would exacerbate already existing discrimination, inequality, and conflict. We need not and should not risk these outcomes.

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[19] International Summit on Human Gene Editing: A Global Discussion, Dec 1-3, 2015 http://nationalacademies.org/gene-editing/Gene-Edit-Summit/index.htm

[20] David Baltimore et al., On Human Gene Editing: International Summit Statement, Dec. 3, 2015 http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a