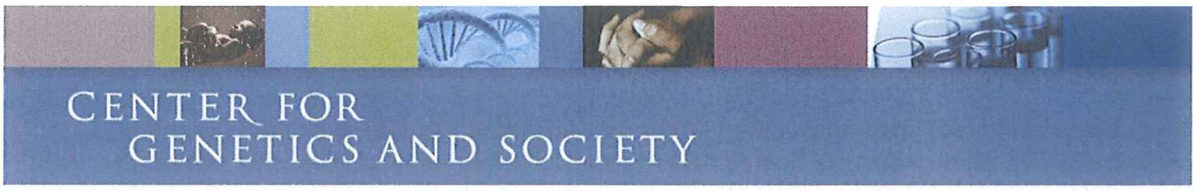


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March 15, 2018

Dr. Maureen Harris
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Sent via email: HRTSR@health.wa.gov.au

Dear Dr. Harris,

Thank you for your invitation to submit comments for the independent review of the Western Australian *Human Reproductive Technology Act 1991*.

These comments are from the Center for Genetics and Society, an independent non-profit public-interest organization based in Berkeley, California, USA. Our mission is 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.

There has been a great deal of development in human genetic and assisted reproductive technologies since the passage of the Western Australian Acts that are now being reviewed. However, many of the social, ethical, and policy considerations that are included as objectives in these Acts are as relevant today as in 1991. In fact, these considerations have acquired even greater significance because of the commercial and other pressures that often accompany increased technical capacities.

Our comments here focus mostly on human gene editing technology, particularly the prospect of its use in human reproduction. We also address "mitochondrial donation" (nuclear genome transfer). Given the continued salience of the safety and social concerns underlying the provisions of the 1991 Act that prohibit human germline modification, we strongly urge that these provisions be retained.

Sincerely,

Marcy Darnovsky

Marcy Darnovsky, PhD
Executive Director

[redacted]

## I. HUMAN GENE EDITING

New gene editing 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 children and subsequent 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 is a critical distinction: 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.

This distinction is recognized in the Western Australian *Human Reproductive Technology Act 1991.* Our understanding is that it also comports with Australian law and policy. It has also 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].

Public opinion aligns with this distinction. Opinion research 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.

A different line that is often invoked in discussion of 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. This means that reproductive germline modification is a matter on

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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

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.

## 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. 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 – both individual and societal – 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.

**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

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[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

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.[7]

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 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

[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 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/

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.

## 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 and some individuals 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,*[8] authored by a committee of the United States 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 claimed a moral objection to PGD. 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.

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.[9]

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."[10] 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

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

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

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

and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.[11]

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.

## II. NUCLEAR GENOME TRANSFER ("MITOCHONDRIAL DONATION" | "THREE-PERSON IVF")

A suite of techniques that would create a human embryo with genetic material from three different people have been referred to by terms including "mitochondrial donation, " "mitochondrial replacement," "mitochondrial manipulation," "mitochondrial transfer," "3-person IVF, " "3-person embryos," "3-parent babies," and "nuclear genome transfer."[12] In these comments, we will use the term "mitochondrial donation," in keeping with the terms of reference for this submission.

The techniques work by transferring the nucleus of an affected woman's egg, or the nucleus of a fertilized embryo, into another woman's enucleated egg or embryo (that is, into an egg or embryo from which the nucleus has been removed but the mitochondria remain). A resulting child would inherit nuclear DNA from the intended mother and father, and mitochondrial DNA from the egg provider.

Thus, mitochondrial donation would not alter the sequence of DNA found either in the nucleus or in the mitochondria of eggs or embryos. Instead, it would recombine intact sequences of mitochondrial DNA and nuclear DNA in gametes or embryos. Like germline gene editing, it is a form of human germline modification. However, because mitochondria are inherited through the maternal line only, it would affect only the progeny of female children born from a gamete or embryo that had been so altered.

The most commonly offered reason to develop and permit mitochondrial donation is to allow a small number of women with a rare kind of severe mitochondrial disease to have a healthy and (mostly) genetically related child. But some scientists are already seeking approval for its use non-disease related infertility.[13] This could open the door to wide-scale embryo genetic engineering for reproduction, absent clear medical necessity.

Critical questions about the safety and efficacy of these techniques have not yet been answered. Many scientists point out that they could have unknown and unforeseeable health consequences for resulting children as well as future generations. One known risk accompanies the mismatch of mitochondrial DNA and nuclear DNA within a cell. A number of studies have concluded that mitochondria play a vital role in nuclear gene expression, so that mismatches could have serious implications for disease susceptibility,

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

[12] Stuart A. Newman, Deceptive Labeling of a Radical Embryo Construction Technique, *Huffington Post,* December 1, 2014 https://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html and Francoise Baylis, Human nuclear genome transfer (so-called mitochondrial replacement): Clearing the underbrush, *Bioethics,* 2017

[13] Jennifer Couzin-Frankel, Unanswered questions surround baby born to three parents, Science, Sep. 27, 2016 http://www.sciencemag.org/news/2016/09/unanswered-questions-surround-baby-born-three-parents

gene expression, and cell function.[14] One study has determined that reversion, the phenomenon whereby carried-over 'faulty' mtDNA multiply faster than donor mtDNA and eventually take over the donor egg, is a serious problem caused by mitochondrial and nuclear DNA mismatch.[15]

In addition, mitochondria do impact inherited traits, so these techniques could lead to unexpected phenotypic outcomes.[16] Another kind of harm, often overlooked, is that the techniques would increase demand for eggs and thus put at risk the health of greater numbers of women.[17]

Notwithstanding these unresolved issues, in February 2015, the United Kingdom approved the clinical use of mitochondrial donation. This approval required a Parliamentary vote to carve out an exception to the UK's wider prohibition on human germline modification.

During the debate about mitochondrial donation in the UK, many observers voiced concern that approval could open the door to additional forms of human germline modification. Indeed, developments since the UK policy was adopted, including the unauthorized birth in Mexico of a child said to be the result of mitochondrial donation techniques, have added weight to that concern. The US-based fertility doctor who undertook this procedure, along with some others working to develop the mitochondrial donation techniques, have openly expressed their goal to commercialize them for age-related infertility. Some also acknowledge their intention and hope that development and use of mitochondrial donation will spur the development and use of germline gene editing.

The UK remains the only country to give regulatory approval for any form of human germline modification. Its policy process has been described as a model for deliberations about reproductive germline editing. In fact, the UK process was flawed in its considerations both of safety and efficacy matters, and social and ethical concerns. Despite a public consultation process, it also downplayed public opposition to approving the procedure.

These issues are closely examined in a recently published article co-authored by a current and a former staff member at the Center for Genetics and Society: Jessica Cussins & Leah Lowthorp, "Germline Modification and Policymaking: The Relationship between Mitochondrial Replacement and Gene Editing," *The New Bioethics*, 2018. https://doi.org/10.1080/20502877.2018.1443409

We are aware of the current campaign by the Australian Mitochondrial Disease Foundation to legalize mitochondrial donation in Australia, modeled in part after the policy process in the UK. In light of the major shortcomings and flaws mentioned above, we do not believe that the UK process should be held up as a model for the legalization of either mitochondrial donation or reproductive gene editing, anywhere in the world.

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[14] Dunham-Snary, Kimberly J. and Ballinger, Scott W., Mitochondrial-nuclear DNA mismatch matters, *Science*, 2015; Gómez-Tatay, Lucía, Hernández-Andreu, José M. and Aznar, Justo, Mitochondrial modification techniques and ethical issues, *Journal of Clinical Medicine*, 2017; Muir, Rebecca, Diot, Alan and Poulton, Joanna, Mitochondrial content is central to nuclear gene expression: Profound implications for human health, *Bioessays*, 2016.

[15] Yamada, M., Emmanuele, Valentina, Sanchez-Quintero, Maria J., Sun, Bruce, Lallos, Gregory, Paull, Daniel, Zimmer, Matthew, Pagett, Shardonay, Prosser, Robert W., Sauer, Mark V., Hirano, Michio and Egli, Dieter, Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes, *Cell Stem Cell*, 2016.

[16] Gómez-Tatay, Lucía, Hernández-Andreu, José M. and Aznar, Justo, Mitochondrial modification techniques and ethical issues, *Journal of Clinical Medicine*, 2017.

[17] Baylis, Françoise, The ethics of creating children with three genetic parents, *Reproductive BioMedicine Online*, 2013.

Please consider the Cussins-Lowthorp article, which we attach, as part of our submission. We also include, at the end of these comments, a short list of articles that expand on our perspective.

## Conclusion

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. There is no need to risk these outcomes. We deeply appreciate the provisions of the Western Australian *Human Reproductive Technology Act 1991* that prohibit human germline modification, and urge that they be retained and strengthened.

### Selected additional resources


Roberto Andorno, Can human germline alterations be ethically justified?, *Bioethica Forum,* September 30, 2017. http://www.bioethica-forum.ch/content/d_AktAusgabe.php

George Annas, A "Better Baby" with Gene Editing?, *Cell,* April 21, 2016. http://www.cell.com/cell/fulltext/S0092-8674(16)30417-2

Françoise Baylis, Human germline genome editing and broad societal consensus, *Nature,* May 8, 2017. https://www.nature.com/articles/s41562-017-0103

Françoise Baylis, Human Germline Gene Editing: An 'Impressive' Sleight of Hand?, *Impact Ethics,* February 17, 2017. https://impactethics.ca/2017/02/17/human-germline-genome-editing-an-impressive-sleight-of-hand/

Françoise Baylis, Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush, *Bioethics,* December 14, 2016. http://onlinelibrary.wiley.com/doi/10.1111/bioe.12309/abstract

Nathaniel Comfort, Can We Cure Genetic Diseases Without Slipping Into Eugenics?, *The Nation*, July 16, 2015. https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/

Marcy Darnovsky, Katie Hasson, and Leah Lowthorp, Reproductive gene editing imperils universal human rights, *OpenGlobalRights*, February 15, 2018. https://www.openglobalrights.org/reproductive-gene-editing-imperils-universal-human-rights/?lang=English

Paul Knoepfler, CRISPR, human genetic modification, & a needed course correction, *The Niche*, June 26, 2017. https://ipscell.com/2017/06/crispr-human-genetic-modification-a-needed-course-correction/

Jim Kozubek, Fixing genes won't fix us, *Boston Globe,* June 1, 2017. https://www.bostonglobe.com/ideas/2017/06/01/fixing-genes-won-fix/A1Q3IZwyyogi6D76Mq6XbM/story.html

Eric S. Lander, Brave New Genome, *New England Journal of Medicine*, July 2, 2015. http://www.nejm.org/doi/full/10.1056/NEJMp1506446

Edward Lanphier, Fyodor Urnov, Ehlen Haecker, Michael Werner & Joanna Smolenski, Don't Edit the Human Germline, *Nature,* 12 March 2015. https://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111

Leah Lowthorp and Marcy Darnovsky, Reproductive Genome Editing and the U.S. National Academies Report: Knocking on a Closed Door or Throwing it Wide Open?, *Bioethica Forum,* September 30, 2017. http://www.bioethica-forum.ch/content/d_AktAusgabe.php

Emily Mullin, The Fertility Doctor Trying to Commercialize Three-Parent Babies, *MIT Technology Review,* June 13, 2017. https://www.technologyreview.com/s/608033/the-fertility-doctor-trying-to-commercialize-three-parent-babies/