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A CALL FOR AN INTERNATIONAL GOVERNANCE FRAMEWORK FOR HUMAN GERMLINE GENE EDITING

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Introduction

From December 1 to 3, 2015, the First International Summit on Human Gene Editing took place in Washington, D.C. to "discuss the scientific, ethical, and governance issues associated with human gene-editing research."[1] Following the 2015 summit, the National Academy of Sciences (NAS) issued the 2017 Report on Human Genome Editing: Science, Ethics, and Governance. The report recognized that risks involved in the field of human genome editing required the addition of new principles and guidance to existing norms, which include the protection of human dignity, "the need for research having scientific and social value," and the related need to generate knowledge that promotes human health.[2] To support the endeavor responsibly, the report has a chapter dedicated to the state of regulatory and international oversight of the field.[3] Notably, the report identified "transnational cooperation" as critical to developing governance in the field, and stresses the "commitment to collaborative approaches to research and governance while respecting different cultural contexts."[4]

To build on relevant discoveries and research as well as continue the international societal dialogue about gene editing, the Second International Summit on Human Genome Editing convened from November 27 to 29,

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1 *International Summit on Human Gene Editing*, Nat'l Acads. Sci., Engineering & Med., http://nationalacademies.org/gene-editing/Gene-Edit-Summit/ (last visited Feb, 8, 2020).

2 Nat'l Acads. of Sci., Eng'g & Med., Human Genome Editing: Science, Ethics, and Governance 31 (2017) [hereinafter 2017 NAS Report] (quoting Council for Int'l Orgs. of Med. Scis. & World Health Org., International Ethical Guidelines for Health-related Research Involving Humans 123 (2016), https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf).

3 *Id.* at 34.

4 *Id.*

2018.[5] During the 2018 summit, varying perspectives emerged surrounding the advisability and ethical implications of moving forward with germline gene editing. Germline gene editing, the topic central to this Note, is the editing of heritable genes that will impact future generations, and as will be discussed, is considered a particularly problematic application of gene editing. One commentator cautiously observed that:

> [M]any of the arguments made against germline genome editing, such as consideration of the autonomy of a child, societal equity, and possible misuse, can be applied as well to other medical technologies, but many jurisdictions have nevertheless permitted those technologies to move forward, so long as they are sufficiently beneficial, safe, and effective.[6]

More skeptical experts noted that germline editing "could be morally permissible in certain circumstances but those circumstances do not yet exist anywhere in the world."[7]

The 2018 summit was heavily impacted by news of Chinese doctor He Jiankui's research, which leaked just before the summit and then was presented at the summit, that he had created the world's first gene-edited human babies through the use of CRISPR-Cas9 (CRISPR) technology.[8] The reaction to this announcement was swift condemnation from the global community, given the undeveloped stage of the technology, regulation, and lack of consensus regarding the implicated ethical issues.[9] David Baltimore of the California Institute of Technology, the chair of the 2018 Summit Organizing Committee, described the occurrence of Dr. He's experiment "a failure of self-regulation by the scientific community."[10]

The failure of this self-regulation is perhaps a consequence of the fact that there is not currently a stronger international regulatory framework or set of principles guiding this subject. There is scant consensus on how to regulate and what to allow, and this is largely because despite the potential

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5 *Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop—In Brief*, 2019 NAT'L ACADS. SCI., ENGINEERING & MED. 1 [hereinafter *Proceedings of a Workshop—In Brief*].

6 *Id.* at 6. This perspective (paraphrased by the source) is attributed to Guido de Wert of Maastricht University. *Id.*

7 *Id.* This perspective (also paraphrased by the source) is attributed to Peter Mills of the Nuffield Council on Bioethics. *Id.*

8 *See* Julia Belluz, *Is the CRISPR Baby Controversy the Start of a Terrifying New Chapter in Gene Editing?*, VOX, https://www.vox.com/science-and-health/2018/11/30/18119589/crispr-gene-editing-he-jiankui (last updated Jan. 22, 2019) ("The stated objective of He's experiment was to disable a gene called CCR5 so the girls might be resistant to potential infection with HIV/AIDS."). A Chinese investigation into Dr. He's experiment found that he had in fact edited the germline of embryos, implanted them in a woman's uterus, and brought them to term, resulting in legal and ethical violations. *See* Austin Ramzy & Sui-Lee Wee, *Scientist Who Edited Babies' Genes Is Likely to Face Charges in China*, N.Y. TIMES (Jan. 21, 2019), https://www.nytimes.com/2019/01/21/world/asia/china-gene-editing-babies-he-jiankui.html?module=inline.

9 *Proceedings of a Workshop—In Brief*, *supra* note 5, at 2–3.

10 *Id.* at 3.

benefits of germline editing, the field is rife with controversy surrounding the "safety concerns, unprecedented informed consent, challenges to human dignity, and the potential for permanent negative impact on future generations, including its abuse for eugenics or enhancement (the parental pursuit of specific traits for non-medical reasons)."[11] There is, however, a general consensus that no clinical applications should proceed until there is "broad societal consensus" involving the opinions of all social groups, perhaps on a global scale.[12]

This Note will argue that human germline editing ought to be subject to a worldwide regulatory initiative contained in an international governance framework. It will touch on the justifications for the call for this agreed upon framework and discuss the current state of regulation of human germline editing, including norms and principles promulgated by international instruments and important statements on the topic. Finally, it will propose suggestions for the substance that an international governance framework should include and acknowledge the challenges in implementing such a framework.

I. What Is Germline Editing?

A. Gene Editing

Gene editing, or genome editing,[13] is a form of genetic engineering that allows scientists to modify genes, thereby changing an organism's DNA.

11 Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing into In Vitro Fertilization*, 12 Reprod. Biology & Endocrinology 1 (2014) (footnotes omitted) (first citing Paul R. Billings et al., *Human Germline Gene Modification: A Dissent*, 353 Lancet 1873, 1873–75 (1999); Mark S. Frankel & Audrey R. Chapman, Am. Ass'n for the Advancement of Sci., Human Inheritable Genetic Modifications: Assessing Scientific, Ethical, Religious, and Policy Issues (2000); Bernard D. Davis, *Germ-Line Therapy: Evolutionary and Moral Considerations*, 3 Hum. Gene Therapy 361, 361–63 (1992); James V. Neel, *Germ-Line Gene Therapy: Another View*, 4 Hum. Gene Therapy 127, 127–28 (1993); then citing Billings et al., *supra*; Frankel & Chapman, *supra*; then citing Johnathan Glover, What Sort of People Should There Be? 45–47 (1984); and then citing Frankel & Chapman, *supra*; Davis, *supra*; C.S. Lewis, The Abolition of Man 69–71 (1965); Paul Ramsey, Fabricated Man: The Ethics of Genetic Control (1970); Michal J. Sandel, *The Case Against Perfect*, Atlantic, April 2004, at 51–62).

12 *E.g.*, 2017 NAS Report, *supra* note 2, at 132; Eric Lander et al., *Adopt a Moratorium on Heritable Genome Editing*, 567 Nature 165, 166 (2019) [hereinafter 2019 Call for Moratorium]; Press Release, Nat'l Acad. of Sci., Engineering, & Med., On Human Gene Editing: International Summit Statement (Dec. 3, 2015), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a [hereinafter 2015 Call for a Moratorium]; *see also* Hervé Chneiweiss et al., *Fostering Responsible Research with Genome Editing Technologies: A European Perspective*, 26 Transgenic Res. 709, 712 (2017).

13 The terms "gene" and "genome" have distinct meanings: "The term 'genome' generally refers to the entire sequence of DNA of an organism. The genome includes genes: sequences of DNA with specific functions that are involved in the production of the proteins needed to carry out many biological roles." *Genome Editing in Brief: What, Why, and How?*, Nuffield Council on Bioethics (Sept. 30, 2016), https://www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review/guide-to-the-report/genome-editing-

Gene editing itself is not a new concept or technology: the first successful gene editing technique was created in 1972 by scientists who discovered how to recombine pieces of DNA to create hybrid sequences.[14] This technique, called recombinant DNA, formed the basis of gene therapy, an experimental treatment that attempts to alleviate or cure diseases by inserting healthy genes into DNA sequences to compensate for problematic ones.[15] Gene therapy as a treatment is currently being researched and developed in clinical trials worldwide, and in certain situations is available for patients seeking clinical treatments.[16]

Despite progress, the recombinant DNA technique was not always consistent or reliable, and could be described as "more of a patch kit than a repair shop."[17] Thus, the advent of CRISPR as a gene-editing tool in 2012 promised to be a game changer for gene editing because of its efficiency and precision in altering, deleting, and adding bits of DNA in living organisms.[18] The protein Cas9 works like "a pair of molecular scissors, capable of cutting strands of DNA" to remove a desired portion of the strand and replace it with a strand that is either healthy or altered in some way.[19]

CRISPR promises to fulfill many different purposes, ranging from food and agricultural applications to human gene editing. With regard to the latter, laboratory and animal studies have demonstrated CRISPR's potential to correct genetic defects, similar to current applications of gene therapies.[20] Another potential application is to use CRISPR to make gene drives.[21] For contextual purposes, an important distinction must be made between gene therapies, which involve somatic cell gene editing, and gene drives, which involve germline editing. Somatic cells are live but nonreproductive cells

in-brief-what-why-and-how. For purposes of this Note, the terms "genome editing" and "gene editing" will be used interchangeably to refer to genetic modification through editing technology, such as CRISPR-Cas9.

14 Ariel Bleicher, *Genome Editing Before CRISPR: A Brief History*, MEDIUM (Oct. 23, 2018), https://medium.com/ucsf-magazine/genome-editing-before-crispr-a-brief-history-f02c1e3e2344.

15 Nat'l Insts. of Health, *What Is Gene Therapy?*, GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/therapy/genetherapy (last visited Feb. 9, 2020).

16 Bleicher, *supra* note 14.

17 *Id.*

18 *See generally* Matthew C. Nisbet, *The Gene-Editing Conversation*, AM. SCIENTIST, Jan.–Feb. 2018, at 15. For an explanation on how the CRISPR-Cas9 system works, see Nat'l Insts. of Health, *What Are Genome Editing and CRISPR-Cas9?*, GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting (last visited Feb. 9, 2020). In basic terms, researchers create a small piece of RNA as a "guide" sequence, attached to the enzyme Cas9, which is designed to target a specific sequence of DNA in the genome. The RNA "guide" recognizes the sequence and the enzyme cuts the DNA at that specified point, at which point researchers can use the cell's repair mechanisms to add or delete parts of the genetic material, or even insert customized DNA. *Id.*

19 Aparna Vidyasagar, *What Is CRISPR?*, LIVE SCI. (Apr. 21, 2018), https://www.livescience.com/58790-crispr-explained.html.

20 *See id.*

21 *See id.*

that inform the genetics of a single individual organism. Somatic cell editing would address a genetic problem affecting only that individual.[22] As will be described in Part III, clinical trials and applications of somatic cell editing have existed in the United States since the 1980s with extensive oversight from regulatory bodies.[23] According to a recent report, over 2600 clinical trials of gene therapies have been approved, in progress, or completed in 38 countries to date.[24]

Germline editing, on the other hand, is the editing of cells which are heritable; thus, the modification made in a germline gene will be inherited by successive generations. Gene drives are an application of germline editing that bias inheritance of a gene in future generations by editing heritable germline cells. As will be briefly discussed in the following Section, research has been conducted on nonhuman applications of gene drives, such as engineering malaria-carrying mosquitos to pass on genes that result in predominantly male offspring, thereby reducing the population, but even this research has not yet resulted in widespread testing.[25] Until Dr. He's experiment, research on human germline editing had been limited to petri dishes or banned, either effectively or directly, in all instances.[26] Furthermore, the summits of 2015 and 2018 both resulted in calls for moratoriums on research involving clinical applications (i.e., where a modified embryo was used to establish a pregnancy) until certain criteria are met.[27] In research and discussions of ethics, the two applications—somatic and germline—are viewed very differently: somatic cell editing, which generally involve gene therapies, broadly has the support of the global scientific and policymaker communities and is on the forefront of medicine.[28] Such applications of gene editing do not pose the same controversies as germline editing, largely because they involve individuals who are already sick, will affect only that consenting patient, and have been more extensively researched. In contrast, there is a general consensus that clinical applications of human *germline* editing should

22 *See Somatic Cell Genome Editing*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCI., https://ncats.nih.gov/somatic (last updated Oct. 1, 2019).

23 *See infra* Part III.

24 Samantha L. Ginn et al., *Gene Therapy Clinical Trials Worldwide to 2017: An Update*, J. GENE MED., May 2018, at e3015, e3015 (2018).

25 Ace North, *Reducing Numbers of Malaria-Transmitting Mosquitoes Using Gene Drive Technology: A Modelling Approach*, BIOMED CENT. (Mar. 29, 2019), https://blogs.biomedcentral.com/on-biology/2019/03/29/reducing-numbers-malaria-transmitting-mosquitoes-using-gene-drive-technology-modelling-approach/.

26 *See* Mary Todd Bergman, *Perspectives on Gene Editing*, HARV. GAZETTE (Jan. 9, 2019), https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/ (discussing Dr. He's experiment, the resulting outcry, and general restrictions that have been placed on human germline editing).

27 *See* 2019 Call for Moratorium, *supra* note 12; 2015 Call for Moratorium, *supra* note 12.

28 *See* Bergman, *supra* note 26.

be "off limits" for now.[29] While somatic gene editing and gene therapies are not central to this Note, they are relevant where their governing regulatory regimes overlap or provide guidance for discussions of the regulation around germline editing.

B. General Applications of Gene Drives and Germline Gene Editing

Gene editing currently occupies a unique space in international headlines, with fears of dystopian worlds ruled by "designer bab[ies]" on the horizon, hopes for the promise of eradication of terrible genetic diseases and disorders, and confusion about how best to proceed with research and clinical applications.[30] However, while the discussion looms large on the topic of human germline editing, nonhuman applications have been in academic, scientific, and policy-based discussions for many years, particularly around the use of gene drives to engineer solutions to environmental and agricultural problems.

A gene drive, which is an application of germline editing, is a method of biasing the likelihood that a certain gene or trait will be inherited by a future generation.[31] Applications of gene drives have thus far been discussed seriously in the context of altering populations of plant and animal species, such as "reprogramming mosquito genomes to eliminate malaria, reversing the development of pesticide and herbicide resistance, and locally eradicating invasive species."[32] One of the most common uses discussed is that of eradicating the mosquito that carries malaria, a venture currently being tackled by Target Malaria, a research consortium largely funded by the Bill and Melinda Gates Foundation, which hopes to begin field testing of CRISPR-edited mosquitos as early as 2024.[33] It would be naïve to emphasize the benefits and promise of gene drives without acknowledging the risks: attempting to alter wild populations could have unintended consequences that could inevitably affect the global commons. In fact, one of the advocates and developers of CRISPR who touted its potential for conservation against invasive species later cautioned that this "inclusion [as a potential benefit] was a mistake: such drive systems lack control mechanisms and are consequently highly invasive."[34] The theoretical and actual perils of being able to engineer and carry out an extinction or permanent alteration of a species require little

29 Katie Hasson & Marcy Darnovsky, *Gene-Edited Babies: No One Has the Moral Warrant to Go It Alone*, GUARDIAN (Nov. 27, 2018), https://www.theguardian.com/science/2018/nov/27/gene-edited-babies-no-one-has-moral-warrant-go-it-alone.

30 *See, e.g.*, Bergman, *supra* note 26.

31 *See* Bruce R. Conklin, *On the Road to a Gene Drive in Mammals*, 566 NATURE 43, 43–44 (2019).

32 Kenneth A. Oye et al., *Regulating Gene Drives*, 345 SCIENCE 626, 626 (2014).

33 Megan Molteni, *Here's the Plan to End Malaria with Crispr-Edited Mosquitoes*, WIRED (Sept. 24, 2018), https://www.wired.com/story/heres-the-plan-to-end-malaria-with-crispr-edited-mosquitoes/.

34 Kevin M. Esvelt & Neil J. Gemmell, *Conservation Demands Safe Gene Drive*, PLOS BIOLOGY, Nov. 16, 2017, at e20003850.

elaboration. An article in *The Economist* ominously titled *Extinction on Demand* summed up the problem of unintended and irreversible consequences: "If drives are engineered into species that play a pivotal but previously unappreciated ecological role, or if they spread from a species of little ecological consequence to a close relative that matters more, they could have damaging and perhaps irreversible effects on ecosystems."[35]

Looking at the potential risks and ethical concerns implicated in the alteration of populations of mosquitos and plants reflects the fact that similar applications in humans merit even closer scrutiny. Interestingly, a 2014 article that advocated for more thoughtful regulation of gene drives largely wrote off the risk of altering the human population as a serious risk posed by gene drives. The authors reasoned that gene drives could not effectively alter the human population because of the human species' long generation times and lack of effective gene editing technologies for humans.[36] Much has changed since the writing of the article. For one, the technological capabilities for human germline editing do exist now. Furthermore, while the authors of the article may be correct to note that gene drives will hardly have the impact in terms of the scale and speed that they might have on mosquito populations, this is not the exclusive, or even central, focus of the conversation around human germline editing. There are many dangers and unknown issues associated with altering heritable genes that will be passed on to future generations, including ethical issues, which are arguably unique to humans.

C. Potential Benefits of Human Germline Editing

CRISPR pioneer Feng Zhang explained the importance of a moratorium on clinical applications and trials of human germline gene editing following the 2018 summit, saying, "Society needs to figure out if we all want to do this, if this is good for society, and that takes time."[37] The question of whether human germline editing is a good thing has yet to be resolved. However, while the risks and ethical mores of germline editing are central to the need for its regulation,[38] there are also legitimate reasons that human germline editing is being seriously explored: its enormous potential for good.

Germline editing could eliminate genes that cause disease, which could positively affect the treatment of illnesses. Somatic gene editing has proven its potential to be a tool for disease treatment and prevention: in 2015, gene therapies were already being used to treat eye disease, and further trials demonstrate that this type of gene editing may be effective in treating certain

35 *The Promise and Peril of Gene Drives*, ECONOMIST (Nov. 8, 2018), https://www.economist.com/briefing/2018/11/08/the-promise-and-peril-of-gene-drives.

36 *See* Oye et al., *supra* note 32, at 627.

37 Bergman, *supra* note 26.

38 *See infra* Sections II.B–C.

blood disorders.[39] With regard to germline editing, screening embryos and using in vitro fertilization is an existing method of avoiding genetically inherited diseases like Huntington's. However, germline editing could potentially completely eliminate these diseases and allow couples who would otherwise fear passing these characteristics to their offspring to parent children genetically related to them.[40]

II. WHY HUMAN GERMLINE EDITING NEEDS A WORLDWIDE REGULATORY INITIATIVE

A. The Global Impact on the Human Species

Human germline editing is "an issue that will ultimately affect the entire species."[41] There are multiple ethical objections to the clinical applications of human germline editing, and indeed, to the research itself. But the reason these issues need to be tackled on a global scale, rather than on an individual state level, is the fact that "[w]hile each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations."[42] Altering the human species transcends geopolitical borders and is not a localized issue.

Furthermore, the consequences and effects of germline editing applications would not and cannot be confined to any one state or region. Movement of persons across borders, family formation, and other human migratory patterns guarantee that genetically modified persons and successive generations will end up dispersed across state borders. In fact, there are already millions of patients who cross borders for the purpose of seeking medical treatment outside their home country or country of residence, motivated by cost benefits or access to better technology.[43] Absent a harmonized set of rules for germline editing, "medical tourism" will inevitably result in persons seeking such procedures to obtain them abroad even if it is not available in their home country. Medical tourism was the cause a relevant high-profile case in the European Court of Human Rights (ECHR) brought by the Mennessons, a French family.[44] Seeking to get around French laws that banned surrogacy, the Mennessons engaged in a surrogacy arrangement in California, where surrogacy is legal. France refused to recognize the parentage of the Mennessons over their twin girls because of the illegality of the

39 Karen Weintraub, *5 Reasons Gene Editing Is Both Terrific and Terrifying*, NAT'L GEOGRAPHIC (Dec. 3, 2015), https://news.nationalgeographic.com/2015/12/151203-gene-editing-terrific-terrifying-science/.

40 *Id.*

41 2019 Call for Moratorium, *supra* note 12, at 166.

42 2015 Call for Moratorium, *supra* note 12.

43 *See generally* Edward Kelley, Medical Tourism, Presentation at the Global Health Histories Seminar 73 (Oct. 2, 2013).

44 *See* Press Release, European Court of Human Rights, Totally Prohibiting the Establishment of a Relationship Between a Father and His Biological Children Born Following Surrogacy Arrangements Abroad Was in Breach of the Convention (June 26, 2014).

arrangement. However, the ECHR intervened because despite the legitimate public policy justifications of France's surrogacy laws, refusing to recognize the legal relationship between the resulting children and their parents violated the children's right to a social identity and possibly implicated other issues such as their citizenship rights.[45]

Mennesson v. France illustrates the issues involved in failing to achieve an international regulatory framework, made particularly problematic where the main parties involved—the resulting children—are completely innocent of the decision made. The issue of international surrogacy tends to demonstrate that where states are not aligned on procedures that will implicate human rights, medical tourism presents ample opportunity for abuse and confusion.[46]

The implications that this type of clinical application could have on the entire human species, the medical risks, and the moral, societal, and ethical issues associated, are shared by all of humankind, regardless of state boundaries and borders. Furthermore, there is an international interest in ensuring that human rights and human dignity are addressed on an international field.

B. Risks Involved in Germline Gene Editing

Legal professor and bioethicist Katherine Drabiak describes the rhetoric around gene editing "intentionally misleading," stating that the current state of technology is not as efficient as it is believed to be in terms of its potential benefits, and that, in fact, there is significant risk involved.[47] The medical risks associated with germline gene editing include mosaicism, meaning some genes contain the intended modification and others do not. This can lead to serious health risks in later stages of development[48] and other off-target effects. Off-target effects "refer to a range of unintended outcomes" that can have serious health impacts on the child, including advanced aging or the development of tumors.[49] Problematically, preimplantation genetic diagnosis (PGD), a process used to test the health of an embryo prior to implantation for pregnancy,[50] often fails to accurately assess the effects of gene editing on an embryo. The inability to use PGD to test the health of an edited embryo would make it difficult to ascertain the germline editing procedure's effectiveness prior to the embryo's implantation. In other words, PGD cannot be used as a safeguard to indicate whether the editing has

45 *Id.*

46 For further discussion on the lessons learned from lack of uniform regulation on the issue of international surrogacy, see Seema Mohapatra, *Adopting an International Convention on Surrogacy—A Lesson from Intercountry Adoption*, 13 LOY. U. CHI. INT'L L. REV. 25 (2015).

47 Katherine Drabiak, *Untangling the Promises of Human Genome Editing*, 46 J.L. MED. & ETHICS 991, 997 (2018).

48 *Id.* at 998.

49 *Id.*

50 *See id.* at 993.

worked correctly prior to implantation.[51] PGD can, however, be used to assess whether a defective gene is present in an unedited embryo, which is why Drabiak points to this as a better alternative to germline editing.[52]

Finally, there are a range of unpredictable effects that may emerge at any point in the future person's life as a result of tampering with their initial germline cells. Drabiak notes that current research touting effectiveness incorrectly presumes that, following a gene editing procedure, "embryo survival equates to health."[53] In other words, a test subject embryo's surviving the trial is not necessarily an indication of how the fetus will fare in the next nine months, or the years and decades following its birth. Some scholars believe that "germline modification will never be safe . . . because interactions between genes are highly integrated, designed to achieve stability and balance, and manipulation of one location risks disrupting the biological equilibrium."[54] Of course, this poses a serious obstacle to any research: with the current expert consensus on a moratorium on any applications that would result in a pregnancy,[55] it is not possible to observe effects of germline editing on later stages of development of a child. Drabiak proposes that these risks are severe enough that they easily outweigh any benefits that germline gene editing could ever theoretically provide.[56]

C. Societal, Ethical, and Moral Considerations

"The ethical assessment of human germline genome editing falls, broadly, into two categories: (1) those arising from its potential failure and (2) those arising from its success."[57] Section II.B provided an overview of the risks and dangers of germline editing procedures. But it bears reiterating that there are ethical considerations implicated in these potential failures of germline editing: the ethical issues involved in the research and clinical applications of a procedure that not only may pose risks and dangers on the life of a nonconsenting individual, including downstream effects that may not materialize until later in his or her development, but that would also invariably impact his or her future offspring.

If these risks and dangers are removed and germline editing is an unconditional success, however, the ethical issues do not go away. On the contrary, the ethical considerations become perhaps even more complex

51 *See id.* at 998.

52 *See id.* at 993. PGD is an option that currently exists for reproductive planning that allows doctors and parents to test embryos for genetic diseases and select embryos without the mutations that might lead to certain diseases. *Id.*

53 *Id.* at 997.

54 *Id.* (citing Stuart A. Newman, *CRISPR Will Never Be Good Enough to Improve People*, 30 GENE WATCH 5, 6 (2017); Stuart A. Newman, *The Hazards of Human Developmental Gene Modification*, 13 GENE WATCH 10, 10–12 (2000)).

55 *See* 2019 Call for Moratorium, *supra* note 12, at 166.

56 *See generally* Drabiak, *supra* note 47.

57 Kelly E. Ormond et al., *Human Germline Genome Editing*, 101 AM. J. HUM. GENETICS 167, 169 (2017).

because they are unprecedented and hypothetical.[58] Even for therapeutic applications (in other words, applications for curing disease), characterizing gene editing as a "means of restoring genomic integrity" invokes undertones of eugenics, "where individuals have a moral obligation to 'scrub deleterious mutations from the germline' as part of a duty to prevent disease that threatens society."[59] The most recently proposed moratorium on clinical application of human germline genome editing, published in March 2019, summarizes the possible societal effects of introducing successful germline editing procedures:

> Individuals with genetic differences or disabilities can experience stigmatization and discrimination. Parents could be put under powerful peer and marketing pressure to enhance their children. Children with edited DNA could be affected psychologically in detrimental ways. Many religious groups and others are likely to find the idea of redesigning the fundamental biology of humans morally troubling. Unequal access to the technology could increase inequality. Genetic enhancement could even divide humans into subspecies.
>
> Moreover, the introduction of genetic modifications into future generations could have "permanent and possibly harmful effects on the species.[60]

The above passage primarily addresses the possibility that the use of germline editing for genetic enhancement would follow if germline editing were to become an acceptable procedure. In terms of acceptability, many distinguish between nontherapeutic genetic enhancement, or gene editing to engineer particular human traits like athleticism or intellect, and therapeutic gene editing, which addresses debilitating or life threatening genetic diseases.[61] Marcy Darnovsky, head of the nonprofit Center for Genetics and Society, believes that "[u]nlike curing disease, genetic enhancement would be morally reprehensible."[62] The 1997 film *Gattaca* provides a cliché, but apt, illustration of the potential societal problems of genetic enhancement and reflects society's fears about eugenics and genetic interventions. In this dystopian not-too-distant future, parents have the option to conceive children through the genetic selection of the best traits of their parents, and the "in-valids"—individuals who were conceived without genetic intervention—occupy a second-class position in society.[63] Despite laws against genetic discrimination, the Gattacan society found ways to relegate inferior employment and social positions to those individuals who were deemed genetically infer-

58 Araki & Ishii, *supra* note 11, at 9.

59 Drabiak, *supra* note 47, at 993 (citing Ifeoma Ajunwa, Address at Data & Society, Databite No. 41: On Genetic Coercion (June 11, 2015), http://opentranscripts.org/transcript/databite-ifeoma-ajunwa-genetic-coercion/?highlight=ifeoma%20ajunwa).

60 2019 Call for Moratorium, *supra* note 12, at 167.

61 *See, e.g.*, Nisbet, *supra* note 18 (sharing survey findings that that eighty percent of Americans would oppose changing genes to improve intelligence or physical traits, whereas only sixty-five percent of Americans would oppose changing genes of unborn babies to reduce their risk of disease).

62 Weintraub, *supra* note 39.

63 GATTACA (Jersey Films 1997).

ior.[64] Even the unrealized potential of such applications demonstrates the necessity of implementing proper regulation before germline editing gets off the ground so that it cannot be abused in these readily imaginable ways. These concerns are related to a commonly invoked principle of the "slippery slope," in which concessions made to allow "acceptable" applications risk permitting unacceptable applications further down the road.[65]

There is also the ethical dilemma about the unnaturalness of germline editing and theologically based concerns that germline editing "amounts to playing God."[66]

> Although allegations of playing God are two a penny in debates about breakthrough technologies, with gene drives they do feel better-founded than usual. The ability to remove species by fiat—in effect, to get them to remove themselves—is, like the prospect of making new species from scratch, a power that goes beyond the past ambit of humankind.[67]

While the idea of causing extinction or making a species from scratch is referencing nonhuman applications of germline editing, the underlying principle—objecting to the tampering with species, including humankind—remains the same, if not possibly even more objectionable in substance. Even nonreligious persons have moral reservations related to this theory of "playing God" that takes the form of objection to the unnaturalness of the idea and how it constitutes a perceived assault on human dignity. A Pew Research study found that over twenty-five percent of nonreligious people opposed gene editing of a baby, even where doing so would improve that baby's health, for the exact same reasons as did people who identified as religious—"because it would be meddling with nature and cross a line that should not be crossed."[68] Bioethicists have used the term the "yuck factor" to describe the intuitive aversion people feel when confronted with the idea of genetic engineering. "The Yuck Factor likely has its origins in Kantian and Christian philosophies of human dignity that permeate Western culture . . . [and] emphasize that human life has a higher moral place than the rest of the natural world."[69]

Another frequently discussed issue is that of consent, not only of a future individual child, but of future generations. In attempting to debunk this argument, professor and ethicist John Harris points out that "[w]e have literally no choice but to make decisions for future people without considering

64 *Id.*

65 *See* 2017 NAS REPORT, *supra* note 2, at 128 ("This continuum almost always starts with converting single-gene disorders to a common, nondeleterious sequence at the most-acceptable end, and moves toward enhancements that are unrelated to disease on the least-acceptable end.").

66 John Harris & Marcy Darnovsky, *Pro and Con: Should Gene Editing Be Performed on Human Embryos?*, NAT'L GEOGRAPHIC (Nov. 26, 2018), https://www.nationalgeographic.com/magazine/2016/08/human-gene-editing-pro-con-opinions/#close.

67 *See The Promise and Peril of Gene Drives*, *supra* note 35.

68 Nisbet, *supra* note 18.

69 *Id.*

their consent."[70] But arguably there is a difference between simply allowing our choices to indirectly affect future generations, and choosing to engage in direct interventions in aspects that will affect the very personhood of future generations.

D. Expert and Public Consensus That Regulation Is Needed

For a combination of all of these reasons, experts across fields with knowledge on the subject of gene editing, and particularly germline editing, are calling for caution. The aforementioned CRISPR pioneer Feng Zhang of the Broad Institute of Harvard and MIT, in supporting a moratorium, noted that before beginning experimentation, society needs to decide if human germline editing is even a good that should be pursued. If that is decided, he said, "we need to have guidelines first so that the people who do this work can proceed in a responsible way, with the right oversight and quality controls."[71] In reaction to Dr. He's revelation at the 2018 summit, David Baltimore, chair of the Summit Organizing Committee, called the fact of the experiment "a failure of self-regulation by the scientific community."[72]

Furthermore, following both the 2015 and 2018 summits, groups of scientists and experts put out calls for a moratorium on clinical applications of human germline editing until a "broad societal consensus" could be reached and an international governance framework established.[73] While this consensus has not been reached and may in fact be far away,[74] presumably there should be a governance framework ready to govern applications prior to this consensus to ensure that society and science proceed with caution, wisdom, and oversight. Furthermore, the development of principles and potential regulatory regimes may in fact help different arms of society come together in dialogue about the issue; in other words, resolving governance issues on the topic may be an important step in achieving this consensus.

E. The Current Existence of Human Germline Editing Capabilities

Finally, the fact that germline editing capabilities are now out of the realm of science fiction puts pressure on their effective regulation, regardless of whether they are currently being applied in a clinical setting. Germline editing, genetic enhancement, and designer babies are not new topics of debate or societal preoccupation (as evidenced by the aforementioned film *Gattaca*) but the "apparent facility with which such modifications can now be

70 Harris & Darnovsky, *supra* note 66.

71 Bergman, *supra* note 26.

72 *Proceedings of a Workshop—in Brief*, *supra* note 5, at 3.

73 *See supra* note 12 and accompanying text; *see also infra* Part IV.

74 *See* Nisbet, *supra* note 18 (referencing several studies that indicate that most Americans are either unsure about or actively oppose germline editing in most contexts).

accomplished has made discussion of the issues more urgent."[75] CRISPR and future gene editing technologies can now deliver edited DNA to human embryos, which could then be implanted and develop into genetically modified children. Some of these methods have already been applied to nonhuman mammals and tested on nonviable human embryos.[76] As will be discussed in Part III, the United States technically has regulatory frameworks in place governing the application of human (and nonhuman) germline editing. However, these regulations were dreamed up in a day preceding the true reality of human germline editing and in fact are primarily written to address gene therapies.[77] Such regulations, as well as a worldwide framework, bear consideration and reconsideration now that this eventuality is upon us.

III. Current Regulatory Framework in the United States

The United States does not have an explicit legal prohibition on human germline editing.[78] This is relatively unusual in the international community, where there are official prohibitions on human germline editing in many countries, including ones that allow human embryonic stem cell research.[79] That said, germline editing does not exactly have a clear path forward in the current U.S. regulatory and political climate.

Current genome-editing protocols and clinical trials in the United States do not have their own regulatory framework and have instead been "absorbed into the preexisting U.S. regulatory framework for gene therapy, whose overview is largely derived from gene transfer studies"[80]—despite the fact that germline editing, while involving similar technologies and techniques, has vastly different consequences and implications.

Research and experimentation that produced that recombinant DNA gene editing on nonhuman subjects began in the 1970s. In response, the National Institute of Health (NIH) established the Recombinant DNA Advisory Committee (RAC) in 1974. The RAC was charged with overseeing the development of an experimental program examining the risks of the recombinant DNA, minimizing their spread to other ecological situations, and devising guidelines to be followed by researchers.[81]

In the 1980s, application of these techniques to human subjects began to be recognized as a possibility, but aimed at somatic, rather than germline,

75 Dana Carroll & R. Alta Charo, *The Social Opportunities and Challenges of Genome Editing*, 16 Genome Biology, Nov. 5, 2015, at 1, art. 242.

76 *See id.*

77 *See infra* Part III.

78 *See* Eileen M. Kane, *Human Genome Editing: An Evolving Regulatory Climate*, 57 Jurimetrics 301, 319 (2017).

79 *See* Araki & Ishii, *supra* note 11, at 8.

80 Kane, *supra* note 78, at 310.

81 *See* Paul Berg et al., *Potential Biohazards of Recombinant DNA Molecules*, 71 Proc. Nat'l Acad. Sci. U.S. 2593, 2593 (1974).

gene editing.[82] Since that time, authorization for clinical trials for human gene transfer face several bureaucratic obstacles and the submissions before and approval of several agencies. Any clinical trial requires submission of a protocol to the RAC, an Investigational New Drug Application (IND) submitted to the FDA, and institutional approvals from the local Institutional Review Board (IRB) and the local Institutional Biosafety Committee (IBC).[83] Gene therapy products require FDA approval, and while gene therapy research has increased and progressed, as of 2017, no gene therapy product has been approved for the U.S. market.[84] Such products have, however, been successfully introduced into the European market.[85]

In response to criticism of the regulatory system's inefficiency, in 2014, the Institute of Medicine (IOM) of the National Academies published a report recommending that the RAC play a less-involved role in the approval of protocols for gene therapies, given that the area was developed enough to have established techniques.[86] The NIH adopted the recommendations, including one that the RAC play a larger oversight role only where *novel* technical issues were involved, and announced a streamlined review process for gene transfer protocols in 2014. This is where germline editing will likely diverge under the current regulatory regime: as an emerging life science technology, such research is likely to continue requiring the original extensive oversight of the RAC.[87]

In 2009, the FDA approved the first ex vivo somatic genome editing clinical trial, and in 2015, the FDA approved the first in vivo editing trial.[88] A few other genome-editing trials have been approved and conducted involving gene-editing technology called ZFN technology.[89] As of 2017, the first human clinical trial involving CRISPR technology could be near.[90] The current regulatory framework has proven adequate for somatic cell genome editing, given its state of research and development as a field.[91] While there is, as of the writing of this Note, no separate set of regulations for germline

82 *See* Kane, *supra* note 78, at 307.

83 *See id.*

84 *See id.* at 308.

85 *See id.*

86 *See* INST. OF MED. OF THE NAT'L ACADS., OVERSIGHT AND REVIEW OF CLINICAL GENE TRANSFER PROTOCOLS: ASSESSING THE ROLE OF THE RECOMBINANT DNA ADVISORY COMMITTEE 80 (Rebecca N. Lenzi et al. eds., 2014), http://www.nationalacademies.org/hmd/Reports/2013/Oversight-and-Review-of-Clinical-Gene-Transfer-Protocols.aspx.

87 *See* Kane, *supra* note 78, at 308 ("[T]he reservation of RAC review for protocols involving novel technical issues will likely mean that any proposed genome-editing protocols will automatically trigger public review by RAC for the foreseeable future (e.g., first RAC approval of a CRISPR-Cas9 human genome-editing protocol).").

88 Ex vivo editing means that the genes are removed from the body before they are "edited." Contrast this with in vivo, which involves delivering the gene directly into a human body.

89 *See* Kane, *supra* note 78, at 309.

90 The trial had been approved by the RAC but not the FDA. *See* Kane, *supra* note 78, at 310.

91 *See id.* at 311.

editing, the 2017 NAS report noted with approval the robustness of the U.S. regulatory regime. Furthermore, "[b]ecause heritable genome editing would involve the use of other assisted reproductive technologies, oversight of its use would likely involve the same statutes and regulations that apply to IVF and PGD."[92]

Once the viability and effectiveness of gene-editing technologies became clear, the question of editing the human germline arose almost immediately. Germline editing in humans requires research on human embryos to be conducted,[93] and herein lies regulatory and ethical obstacles. Two interdependent questions of propriety are raised: First, and central to the prior discussion in Part II, is whether editing the human germline is appropriate in the first place. Second, and central to the policy and regulatory environment in the United States, is how to regulate the research required for germline editing where it involves human embryos.[94]

It is this second question that has had the greatest impact on advancement of research in the United States. The field is constrained by legislative and other political reactions to the ethical issues and the policy debate around the subject of editing or performing tests on human embryos. These constraints include the Dickey-Wicker amendment, which prohibits the use of federal funds for most types of human embryo research and has been part of federal appropriations bills since 1996.[95] In 2015, Congress reacted to first reports of genome editing in human embryos by adding a specific amendment to the 2015 appropriations bill prohibiting the FDA from using any federal funds to take administrative action regarding "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[96] In 2017, the first U.S. study on genome editing of viable human embryos was published, and a few other experiments have been published since then.[97] Thus, there has been research on germline editing in the United States, but this research has been privately funded.

IV. International Instruments on Human Germline Editing and Related Topics

While individual countries, like the United States, may have laws and regulations addressing research and clinical applications of gene editing, the current state of the *global* dialogue on human germline editing consists of conventions, commentaries, treaties, and other official statements. This Part will provide an overview of the international instruments that represent the current state of international dialogue on the subject. It will discuss the uni-

92 2017 NAS Report, *supra* note 2, at 131.

93 *See* Kane, *supra* note 78, at 311–12.

94 *See id.* at 312.

95 *See id.* at 313, 319 ("[The amendment] bans the use of federal funds to create embryos for research or for research in which an embryo is destroyed or discarded.").

96 Consolidated Appropriations Act of 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2283 (2015).

97 *See* Kane, *supra* note 78, at 312–13.

fying norms regarding germline editing in hopes of taking helpful learnings from these instruments to make suggestions for an international governance framework on human germline editing.

A. Oviedo Convention of 1997 (Europe)

The Convention on Human Rights and Biomedicine of 1997, more commonly known as the Oviedo Convention, is a treaty for the protection of human rights in the biomedical field, and includes provisions for the protection of patient rights and biomedical research issues, including genetics and organ transplantation.[98] While the only signatories are the Council of Europe and other European states, the Oviedo Convention represents the first legally binding international treaty that addresses biomedicine in the field of human rights, which notably includes genetic research and gene editing. Like several international conventions on the topic, it bases its principles on the protection of human dignity and rights, but unlike those other agreements, it goes beyond such broad principles by setting minimum standards with which members are required to comply.[99] These minimum standards include a nondiscrimination provision on the basis of a person's genetic heritage[100] and provide that genetic modification should only be taken for "preventive, diagnostic or therapeutic purposes."[101] Importantly, the Oviedo Convention includes a prohibition on germline editing, specifically disavowing gene editing that will impact a person's descendants,[102] and prohibits the use of medically assisted procreation to choose a child's sex.[103]

B. UN Universal Declaration on Human Genome and Human Rights of 1997

The United Nations (UN) Universal Declaration on the Human Genome and Human Rights of 1997 (the UN Declaration of 1997) lays out a set of principles regarding research and other treatments involving the human genome meant to help guide the development of further regulations, laws,

98 Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Apr. 4, 1997, E.T.S. No. 164 [hereinafter Oviedo Convention].

99 *Id.* art. 27 ("None of the provisions of this Convention shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated in this Convention."). The Oviedo Convention is not without criticism, however. *See Human Rights in Biomedical Field: Concern over the Oviedo Convention*, CONF. EUR. CHURCHES (Oct. 16, 2018), http://www.ceceurope.org/human-rights-in-biomedical-field-concern-over-the-oviedo-convention/ (discussing calls for withdrawal of one of the Convention's protocols for discriminating against persons with mental disorders).

100 Oviedo Convention, *supra* note 98, art. 11.

101 *Id.* art. 13.

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

103 *Id.* art. 14.

and policies at the national and international level.[104] The declaration itself does not contain developed or specific rules; rather, it references "national law" in order to first and foremost keep all research under the oversight of states. For example, it states that "[r]esearch, treatment, or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law."[105]

However, the declaration does condemn "[p]ractices which are contrary to human dignity, such as reproductive cloning of human beings,"[106] and invites states and international organizations to "identif[y] such practices . . . [and take] the measures necessary to ensure that the principles set out in this Declaration are respected."[107]

C. NAS International Summit on Human Gene Editing 2015 and Subsequent NAS Report 2017

From December 1 to 3, 2015, the National Academy of Sciences held the First International Summit on Human Gene Editing, which "convened experts from around the world to discuss the scientific, ethical, and governance issues associated with human gene-editing research."[108] Following the presentations, reports, and other research presented at the summit, in 2017 the Committee on Human Gene Editing published a report summarizing the proceedings and relevant findings, and included recommendations for proceeding with research and experimentation of human genome editing.[109] The report details the current state of regulatory, governance, and ethical issues surrounding human genome editing, and endorsed the current proceedings of somatic cell genome editing in humans. Notably, it took a measured stance with regard to germline editing, noting that "[h]eritable germline genome-editing trials must be approached with caution, but caution does not mean they must be prohibited."[110]

Importantly, this report has an entire chapter dedicated to the state of regulatory and international oversight of the field and principles for governance.[111] The report details seven general principles necessary to promote the safe, effective, and ethical research of human genome editing.[112] These

104 Universal Declaration on the Human Genome and Human Rights, Nov. 11, 1997, UNESCO Gen. Conf., 29th Sess., *endorsed by the United Nations in* G.A. Res. 53/152 (Dec. 9, 1998) [hereinafter the UN Declaration of 1997].

105 *Id.* art. 5.

106 *Id.* art. 11.

107 *Id.*

108 *International Summit on Human Gene Editing*, *supra* note 1.

109 2017 NAS REPORT, *supra* note 2, at 189.

110 *Id.* at 134.

111 *Id.* at 29.

112 These principles are: (1) promoting well-being, (2) transparency, (3) due care, (4) responsible science, (5) respect for persons, (6) fairness, and (7) transnational cooperation. *Id.* at 33.

principles are intended to guide the development of an emerging field of technology and provide considerations for navigating tricky technical, ethical, legal, and policy-oriented questions. Of note, the seventh principle is "transnational cooperation" and stresses the "commitment to collaborative approaches to research and governance while respecting different cultural contexts."[113] These principles support the idea of implementing an international governance framework. With regard to governance, the report recommends a comprehensive list of predicate conditions that must be met prior to proceeding with germline genome editing,[114] concluding that the U.S. regulatory system currently provides adequate oversight of genome-editing research and can serve as a model of a regulatory regime.[115]

Finally, the report included the common refrain for a moratorium—a statement from the organizers of the summit that the organizers of the 2015 summit (described further below in Section IV.D) "call[ing] for a pause of some undefined duration in any attempt at heritable genome editing" until a "broad societal consensus" had been reached on a global scale.[116]

D. The Call for a Moratorium on Clinical Application in 2015

In 2015, the organizing committee for the International Summit on Human Gene Editing in 2015 called for a moratorium on clinical applications involving alteration of the human germline genome through gene-editing technology.[117] The group declared that until there was a consensus about the proposed application of gene-editing technologies, it would be "irresponsible to proceed."[118] Importantly, these scientists also called for an ongoing forum for a global dialogue of the issue:

> 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.[119]

It is important to note that these scientists did not call for an absolute moratorium on research and experimentation; in fact, they noted that "[i]ntensive basic and preclinical research *is clearly needed and should proceed*, subject to appropriate legal and ethical rules and oversight" to gain a better

113 *Id.* at 34.

114 *See infra* Section V.C.

115 *See* 2017 NAS REPORT, *supra* note 2, at 59. For an overview of the U.S. regulatory system for gene editing, see *Kane*, *supra* note 78, at 311–23.

116 2017 NAS REPORT, *supra* note 2, at 132 (quoting 2015 Call for Moratorium, *supra* note 12).

117 Nicholas Wade, *Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited*, N.Y. TIMES (Dec. 3, 2015), https://www.nytimes.com/2015/12/04/science/crispr-cas9-human-genome-editing-moratorium.html.

118 2015 Call for Moratorium, *supra* note 12.

119 *Id.*

understanding of risks, benefits, and ways forward with clinical use.[120] However, this research should only proceed provided that where research results in modified human embryos or germline cells, those modified embryos or cells are not used to establish a pregnancy.[121]

E. NAS International Summit on Human Genome Editing 2018

In November 2018, the Second International Summit on Human Genome Editing was held in China, bringing together over five hundred stakeholders including scientists, ethicists, policymakers, medical professionals, and patient group representatives. The purpose was to continue the discussion called for by the first summit to explore risks and benefits, consider regulatory and policy perspectives, and ethical and cultural considerations.[122]

This summit raised the stakes around these discussions, of course, after Dr. He announced that he had used edited embryos to establish a pregnancy, which had resulted in twin girls. The experiment was condemned for violating several international and ethical norms, but notably revealed not only the gaps in international governance around this issue,[123] but also a clear consensus that the world is not ready for such clinical applications.

F. Call for a Moratorium 2019

In response to events at the 2018 summit, on March 13, 2019, the organizers of the summit published a renewal of the call for a moratorium on clinical applications of human germline genome editing.[124] The authors recalled the moratorium proposed in 2015, but noted that "subsequent events suggest that this [initial] statement was inadequate."[125] The authors further noted that no mechanism had been created to "ensure international dialogue about whether and, if so, when clinical germline editing might be appropriate."[126]

Interestingly, this second call proposes what is probably the most specific and robust "international framework" to guide the development of the discussion and creation of governance for human germline gene editing that exists today. While the proposal does not institute specific rules or guidelines for implementing regulation, it acknowledges and justifies this big picture approach, stating that a "purely regulatory approach will [not] suffice, because it cannot address many of the fundamental questions."[127] The

120 *Id.* (emphasis added).
121 *See id.*
122 *Proceedings of a Workshop—in Brief*, *supra* note 5, at 1.
123 This is reflected in the reactions to Dr. He's experiment by experts and attendees. *See id.* at 2–3.
124 2019 Call for Moratorium, *supra* note 12.
125 *Id.*
126 *Id.*
127 *Id.*

authors also rejected an international treaty, instead favoring a voluntary pledge by nations to not allow any clinical application of germline editing until certain requirements are met for a system of governance and oversight. Suggestions for these requirements include a five-year fixed-period moratorium while more research is collected, and the creation of an international coordinating body. This body could assess "broad societal consensus," create an international panel that serves as oversight, and provide states with comprehensive and objective information through issuance of periodic reports.[128]

V. Necessary and Proper Substance and Design for an International Governance Framework

The numerous international instruments and commentaries already in existence repeat a few essential phrases and ideas. First, clinical applications of gene editing on the human germline should not proceed until there is a "broad societal consensus" on the proposed application of the gene-editing technology.[129] Second, no clinical application should take place until risks and benefits have been properly assessed. These risks include medical risks to the immediate and future descendants that would inherit an edited human genome germline; the societal, ethical, and moral risks; and even the risk of permanent alteration and damage to the human species. Interestingly, the commentary suggests that consensus supports the research of germline gene editing so long as the embryos are not used to establish a pregnancy, presenting a serious obstacle to the development of later stages of research.[130] In other words, given the unpredictable nature of the risks as described by Drabiak—many of which may be impossible to accurately or adequately assess without allowing gene-edited embryos to proceed into later stages of development—it is understandable that some researchers have asserted that germline editing "will never be safe."[131] This is supported—or actually heightened—by the fact that germline editing is irreversible by nature, making any "mistakes" which reveal themselves in future children impossible to rectify.[132]

128 *Id.*

129 *See* Chneiweiss et al., *supra* note 12, at 712 ("At the present time, there must be opposition to any demands for the modification of the related legal framework, in so far as clinical applications are concerned . . . until consensus has been reached with multiple partners throughout civil society."); 2019 Call for Moratorium, *supra* note 12, at 167 ("[C]linical germline editing should not proceed for any application without broad societal consensus on the appropriateness of altering a fundamental aspect of humanity for a particular purpose."); 2015 Call for Moratorium, *supra* note 12 ("It would be irresponsible to proceed with any clinical use of germline editing unless and until . . . there is broad societal consensus about the appropriateness of the proposed application.").

130 *See* 2019 Call for Moratorium, *supra* note 12; Drabiak, *supra* note 47, at 997–99.

131 Drabiak, *supra* note 47, at 997.

132 *See id.* at 998 ("That is, what is to be done with the experiments gone wrong—future persons—who suffer health deficits arising from such germline intervention? Despite Steven Pinker's dismissive guarantee 'of course we would not create embryos with the

Finally, these instruments call for international collaboration toward establishing norms and a guiding framework. The 2019 call for a moratorium represents one of the most robust set of suggestions for an approach that the international community could take with regard to establishing norms and a guiding framework for human germline editing. Notably, there is an express distinction made between somatic and germline editing, as well as between research and clinical applications of germline editing. While *clinical* applications and trials of *germline* editing at this point are generally considered to be unacceptable, research could responsibly proceed, according to these experts, "provided that these studies do not involve the transfer of an embryo to a person's uterus."[133] These experts also noted that with regard to international governance, a "purely regulatory approach will [not] suffice"[134] because of the narrow mandates of regulatory agencies. The UN Declaration of 1997 similarly puts the onus on individual states and national law to carry out the specific aspects of implementing a set of unified international guiding principles.[135]

An international governance framework must above all emphasize the principle of human dignity, mentioned in most of the existing instruments discussed in Part IV, as well as identify some of the most pressing controversies and provide guidelines so each state can tailor their regime while maintaining minimum standards. However, the design of an international governance framework, as noted by the authors of the 2019 call for a moratorium, should aim to give guidelines, and in some cases, set outer limits, that then ultimately allow each state to implement the overarching norms in a tailored manner into their own individual societies and legal systems. Part V will attempt to flesh out the most important elements that should be present in an international governance framework. It will describe the substance of concrete commitments that could be made by the international community so that this framework is capable of fitting different societies and evolving with new technologies, consensus, and needs of the field.

A. Agreement to Seek Broad Societal Consensus.

Experts have emphasized that a clear consensus ought to be reached before any clinical applications or trials of germline editing should proceed at all.[136] Broad societal consensus must involve a "wide range of voices . . . equitably engaged from the outset,"[137] but may be difficult to measure and achieve. In terms of incorporating a "broad societal consensus" requirement into an international governance framework, the issue is difficult from a defi-

probability of being sick and deformed,' one can imagine future persons injured by these experiments would not be assuaged by these cavalier promises.").

133 2019 Call for Moratorium, *supra* note 12, at 166.

134 *Id.* at 167.

135 UN Declaration of 1997, *supra* note 104.

136 *See* 2019 Call for Moratorium, *supra* note 12, at 167.

137 *Id.*

nitional as well as a practical standpoint: What does a broad societal consensus look like, and how is it achieved?

One of the problems with achieving consensus is that much of society still does not know what germline gene editing *is*, much less how they feel about it, inhibiting the ability to comprehend fully and then assess its broader implications.[138] Thus, a governance framework should establish guidelines for (1) achieving societal consensus, which might include a process for informing the public, such as through consistent reporting on multiple perspectives and developments of the technology and its risks, benefits, and ethical ramifications;[139] (2) measuring of societal consensus; (3) establishing timelines for checking "approval" levels; and (4) deciding the steps to be taken depending on the approval level. The 2019 call for a moratorium suggests a five-year waiting period for this dialogue to develop.[140] Societal approval may mean forging ahead, and consistent ambivalence may mean maintaining the current holding pattern as the technology and research develop. A trickier question would arise if society decided it disapproved: Does disapproval mean abandoning all efforts to investigate and implement germline editing into medical procedures? And finally, broad societal consensus must address not only the acceptability of germline editing in the first instance but also the line between acceptable and unacceptable applications of human germline editing.

B. Creation of Standards Distinguishing Between Acceptable and Unacceptable Applications

As a related part of achieving consensus, an international framework should put forth suggestions for acceptable and unacceptable applications of germline gene editing as a procedure. As an initial matter, to generate this list of applications it must be taken as given that it will one day be acceptable to use germline editing to allow a couple to biologically conceive their own child. Otherwise, germline editing to prevent genetic diseases would not be necessary; individuals that wish to become parents have a range of existing alternatives such as PGD, adoption, or surrogacy, that would similarly prevent those parents from passing on any congenital defects.[141]

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138 Surveys have revealed that forty percent of Americans are "not sure" whether it is morally acceptable or not to gene edit babies to give them a reduced risk of disease. Nisbet, *supra* note 18. Forty-two percent of Americans know "nothing at all" on the subject of germline modification and only nine percent admit to knowing "a lot." *Id.*

139 *See id.* (making a case for news organizations as an avenue for "provid[ing] the information, frames of reference, and narratives that scientists, journalists, funders, policy makers, and societal leaders frequently draw upon to set policy, make decisions, or communicate with various segments of the public who trust their advice").

140 2019 Call for Moratorium, *supra* note 12, at 168.

141 *See* Harris & Darnovsky, *supra* note 66 ("It is true that a few couples—a very small number—would not be able to produce unaffected embryos, and so could not use PGD to prevent disease inheritance. Should we permit germline gene editing for their sake? If we did, could we limit its use to cases of serious disease risk?").

One such distinction between acceptable and unacceptable applications might be preventive and therapeutic versus genetic enhancement procedures. To borrow an idea from the Oviedo Convention, a governance framework could allow germline editing only where it would serve a "preventive, diagnostic or therapeutic" function with regard to a heritable genetic disease. However, even the complexity of disease prevention must be acknowledged.[142] Single-gene disorders, caused by the mutation or change occurring in a single DNA sequence, such as cystic fibrosis, Huntington's disease, and sickle cell anemia, can be fatal and seriously reduce the quality of life of suffering individuals.[143] Given that they only affect a single-gene inheritance, they could also potentially be straightforward to address through germline editing.[144] There are other diseases, such as arthritis, heart disease, and cancer, that are the result of multifactorial inheritance, meaning they are caused by the combination of environmental factors and multiple heritable traits.[145] Such diseases may pose greater difficulty in editing and are less certain to manifest, or may have alternative treatment options available if they do.[146] These line-drawing questions are inextricably linked with ethical quandaries, including ones that are "particularly important from a disability rights perspective."[147] "One open question is where to draw the line between disease treatment and enhancement, and how to enforce it, considering differing attitudes toward conditions such as deafness."[148]

Because societal consensus and morality, as well as technical developments in the field, are not static, it would be advisable to include a method of determining where the line for applications should be drawn so that it cannot be abused. How should germline-editing applications respond to these different diseases? An international framework should address this question by putting forward a flexible method, based on factors such as certainty of manifestation, the preventative potential of a genetic treatment, and availability of existing treatments for the disease, to help answer this question.

From the outset, the absolute outer limit of acceptable applications should be firmly established. Part of this line drawing, or identifying a method by which to determine where the line goes, will involve identifying the potential problems with germline editing as a preventative measure and as a tool for genetic enhancement, and being prepared to ask and answer forward-thinking questions. For example, how can we ensure that germline editing will not exacerbate inequalities or become a tool for discrimination?

142 Oviedo Convention, *supra* note 98, at 4.

143 Melissa Conrad Stöppler, *Genetic Diseases (Disorder Definition, Types, and Examples)*, MEDICINENET, https://www.medicinenet.com/genetic_disease/article.htm#what_is_a_genetic_disease_how_is_it_defined (last visited Feb. 9, 2020).

144 *See* 2017 NAS REPORT, *supra* note 2, at 19.

145 Stöppler, *supra* note 143.

146 For a discussion on how different genetic peculiarities affect how germline editing might respond in treatment, see 2017 NAS REPORT, *supra* note 2, at 117–18.

147 Harris & Darnovsky, *supra* note 66.

148 Bergman, *supra* note 26.

One of the ethical issues that germline editing threatens to pose is that inequality will be enhanced by the creation of genetically superior humans. If genetic enhancement is ultimately approved of, will such offerings only be accessible to the elite? Will genetic enhancement be restricted to seemingly "innocent" purposes, such as choosing eye color? And what does innocent mean? Purely cosmetic?

The use of germline editing for genetic enhancement is so fraught that at the outset, use of germline editing for genetic enhancement purposes should be considered the outer line that should not be crossed. Such a prohibition is supported by the 2017 NAS report,[149] and the 2019 call for a moratorium notes that "[g]enetic enhancement of any sort would be unjustifiable at this time."[150] This may change as technology develops, but the debate over the balancing problem between individual freedom (for example, to choose to use an existing germline editing procedure for genetic enhancement purposes) and societal interests (such as the societal interest in prohibiting such an application) may be better suited for a later date. Such problems have historically played out in U.S. civil rights jurisprudence and legal decisions, "which compare the burdens on individual liberties or the discriminatory impact of those burdens to whether there is a rational or compelling need for these particular state restrictions."[151]

C. Establish Preconditions for Experimentation and Clinical Trials

An international governance framework should include suggestions for predicate conditions prior to conducting clinical trials so that research conducted is appropriate to societal consensus, as well as with regard to the safety and efficacy of the technologies. These preconditions could be adopted from the 2017 NAS report, which recommends a comprehensive list of predicate conditions that should be met prior to proceeding with human germline editing:

- the absence of reasonable alternatives;
- restriction to preventing a serious disease or condition;
- restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to that disease or condition;
- restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;
- availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures;
- ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;
- comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy;
- maximum transparency consistent with patient privacy;

149 2017 NAS Report, *supra* note 2, at 13.
150 2019 Call for Moratorium, *supra* note 12, at 166.
151 2017 NAS Report, *supra* note 2, at 119.

- continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and
- reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.[152]

Notably, some of these conditions, including the "availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures,"[153] would be impossible to meet in today's state of regulation and stage of research on the subject. Experts have further noted that morally permissible circumstances for germline editing could potentially exist, but do not yet in any jurisdiction.[154] These predicate conditions address many of the concerning risks that have been discussed: restriction to life-saving application and ensuring that any benefits are strong enough to outweigh the risks. It goes without saying that no clinical trials or applications should proceed until the safety and efficacy of the procedures are reasonably sure. A set of preconditions would help to ensure that research and experimentation proceed responsibly and within previously agreed upon boundaries.

D. Recommendation for a Regulatory Regime and Approval Process for Research and Clinical Applications

If the time comes for clinical trials to proceed, there must be adequate oversight over any such applications. Thus, an international governance framework should include a recommendation for oversight of any research and clinical applications of human germline editing in the form of a robust approval process by regulatory bodies. The 2017 NAS report concludes that the U.S. regulatory system currently provides adequate oversight of genome-editing research, and thus could provide a starting framework to other individual jurisdictions for germline editing.[155] An international governance framework may detail the level of regulation that should be required and hold out robust regulatory regimes as an example for any countries that have not yet implemented such regimes. The recommendation could include a note about designing regulations that restrict clinical applications but are not so strict as to stifle discovery and research. Many countries currently have in place prohibitions that prevent even the research of germline editing (given its effect on human embryos).[156] But as countries begin to explore allowing research to proceed there should be guidelines available for how to do so responsibly. This will allow countries to proceed with research to the level of their comfort with regard to individual cultural, social, and scientific norms.

152 *Id.* at 134–35.

153 *Id.* at 134.

154 *See Proceedings of a Workshop–in Brief*, *supra* note 5, at 6.

155 *See* 2017 NAS REPORT, *supra* note 2, at 59.

156 *See* Araki & Ishii, *supra* note 11, at 8.

E. Establish an International Coordinating Body

The 2019 call for a moratorium makes a crucial suggestion that will not only help to harmonize international norms and principles about the acceptability of applications and achieve societal consensus, but also provide oversight over future dialogue, research, and applications: the creation of an international coordinating body on human germline editing.[157] This body could assess broad societal consensus and create an international panel that provides states with comprehensive and objective information through issuance of periodic reports.[158] The makeup of the body would be a diverse group of interdisciplinary experts from multiple countries, tasked with compiling recommendations on best practices, reporting on progress of the technology and broader society's dialogue, and ensuring transparency with decisions that have a potential global impact. Finally, this group could be constantly reevaluating the international governance framework to identify gaps, address unforeseen issues as they arise, and implement additional preconditions as the day for widespread clinical trials approaches. Most of all, this group could serve as a neutral body representing a unification of global efforts and help to prevent competitive races to the technology among different states. After all, "no individual or organisation—no scientist or fertility doctor, no biotech company or fertility clinic, no advisory committee or bioethics council or scientist-dominated summit—has the moral warrant to skip over these minimum criteria and try to hurry things along."[159]

Conclusion: Challenges to International Governance Framework and the Way Forward

International agreement can be difficult to achieve, and global trends of nationalism and isolationist attitudes tend to exacerbate these difficulties. However, even aside from this, achieving an international regulatory framework on a new technology and capability poses several challenges. For one, the idea of broad societal consensus is touted as an important step moving forward. But what does a broad societal consensus look like on a global scale? It will be difficult enough to establish or measure consensus in one society, and cultural and societal differences threaten to make true global consensus next to impossible to achieve. For example, U.S. society may decide that it is acceptable to use germline editing to allow parents to choose the sex of their child, but for other countries more fraught with gender inequalities and historical controversy about a child's gender, such as India and China, such an application may pose an insurmountable ethical dilemma. Another challenge with approaching the question is that bioethics around medical interventions do not address human germline editing as a preventative measure. After all, most of Western medicine involves intervening with

157 2019 Call for Moratorium, *supra* note 12, at 168.

158 *Id.*

159 Hasson & Darnovsky, *supra* note 29.

nature and thus medical interventions have their own code of ethics,[160] but "[b]y definition, germline gene editing would not treat any existing person's medical needs."[161] This means that the ethics surrounding germline editing may have to be developed from a point further back than many realize.

If a worldwide regulatory initiative is not possible, how should the United States and other countries proceed? The United States should keep in place the existing regulatory regimes (which have been approved of by the 2017 NAS report) and begin to encourage discussions about the desirability of human germline editing and where the line should be drawn between acceptable and unacceptable applications. If nations are forced to go it alone with regard to developing norms and regulations for human germline editing, a crucial question will be how to handle issues such as medical tourism, immigration, and other consequences of a global and mobile world. This may require looking to other areas where there is a lack of universal consensus on topics concerning alternative reproductive technologies, and where states and enforcement bodies have succeeded and failed, such as with international surrogacy as illustrated in the *Mennesson* case.[162]

While the medical risks can be ascertained, it is difficult to know whether the ethical and social fears are overblown. After all, while germline editing capabilities exist, they are, broadly speaking, yet untested and undeveloped. At the same time, different countries are moving forward with germline research, and to different extents. While condemned by the scientific community and by the Chinese government, Dr. He is a cautionary tale for what may happen absent adequate oversight and established norms. In response to Dr. He's experiment, which may have used government funds and banned techniques, China has proposed regulations for human gene editing.[163] Other countries are not far behind allowing germline editing: in 2018, Japan released draft guidelines that would allow gene editing in human embryos (though they would still restrict the use of these embryos for reproduction).[164]

With these developments, broader questions—for example, can society be trusted to handle these capabilities responsibly and in a way that does not result in a *Gattaca*-like dystopia?—almost appear to be moot. Now that the capability exists, it seems unlikely that there is any choice but to address problems that will arise. Dr. He's experiment may have served as a catalyst for the creation and implementation of regulations such as those proposed in Japan and China, but the international community should not wait for

160 *See Code of Medical Ethics Overview*, AM. MED. ASS'N, https://www.ama-assn.org/delivering-care/ethics/code-medical-ethics-overview (last visited May 5, 2019).

161 Harris & Darnovsky, *supra* note 66.

162 *See supra* note 44 and accompanying text.

163 *See* Jef Akst, *China Proposes New Gene-Editing Regulations*, SCIENTIST (Feb. 27, 2019), https://www.the-scientist.com/news-opinion/china-proposes-new-gene-editing-regulations-65544.

164 David Cyranoski, *Japan Set to Allow Gene Editing in Human Embryos*, NATURE (Oct. 3, 2018), https://www.nature.com/articles/d41586-018-06847-7.

another global ethical and scientific disaster to retroactively try to address the problems posed by germline editing. Given the global nature of the issue, the ethical and social issues that transcend state lines, and the potential impact on the human species, there should be an international governance framework that helps to harmonize norms, and which prods states to develop these norms together when it comes to human germline editing. Proactive development of such a framework and thoughtful engagement in dialogue will be essential to ensuring, if society decides to move forward, that any applications of this potentially treacherous technology will, instead of posing bewildering and dangerous ethical and medical dilemmas, be conducted responsibly and in a way that ultimately benefits humankind.