Is current US regulation of germline CRISPR editing effective or should a moratorium be placed on all research in the area in the future?

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The alteration of various traits in humans has been a science fiction dream for over a century. Films like Gattaca and Elysium have captured th imagination of many. With the discovery of CRISPR - CAS 9 in 2012, what used to be fiction is now close to reality. The future of medicine is already here. The clustered regularly interspaced short palindromic repeat (CRISPR)-Cas system is currently regarded as "the most reliable tool for genome editing and engineering" according to Ishino et al 2018.[1] The unique CRISPR sequence was first discovered over 30 years ago by Y. Ishino in *Escherichia coli*, however the exact function of the sequence was not uncovered until the mid-2000s.[2] There were initially three classes of Cas systems discovered: Type I was Cas3, Type II was Cas9, and type III was Cas10. The second type was proven to be most effective for genome editing as it could work well with both CRISPR RNA and the trans-activating CRISPR RNA.[3] The structure and function of the CRISPR-Cas9 system can be seen in Figure 1.

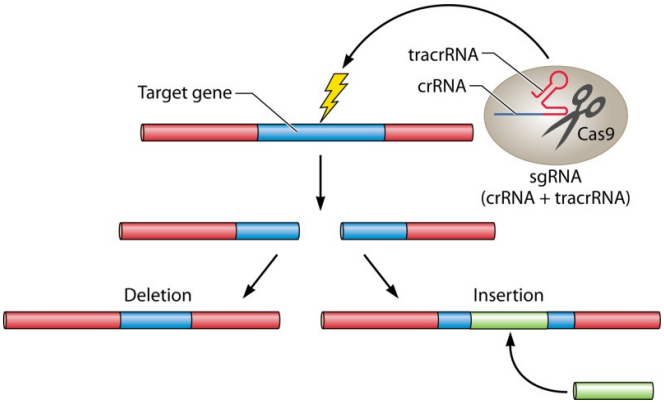

Figure 1: Genome editing by CRISPR-Cas9.[4]

The CRISPR-Cas9 system works as a pair of scissors, cleaving the double-stranded DNA at the intended position on the genome. The CRISPR RNA (crRNA) which has a sequence homologous to the intended target, along with the trans-activating CRISPR RNA (tracrRNA) both act as the guiding mechanism to bring the Cas9 nuclease to the target site. The Cas9 complex acts as the "blade" which allows the gene to be cleaved. Thus it is easy to disrupt the function of the gene by a simple insertion or deletion.[5]

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1 Yoshizumi Ishino, Mart Krupovic, and Patrick Forterre, "History of CRISPR-Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology," *Journal of Bacteriology*, January 22, 2018, Page 1.

2 Yoshizumi Ishino et al., "Nucleotide Sequence of the Iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia Coli, and Identification of the Gene Product.," *Journal of Bacteriology*, 1987.

3 Yoshizumi, 2018.

4 Yoshizumi, 2018.

5 Yoshizumi, 2018.

Since its discovery as a genome cleaving mechanism in the 2010s, CRISPR has been used for a wide variety of purposes such as the correction of a mutation associated with Hereditary Tyrosinemia Type 1 (HTI) and the editing of the CFTR gene in Cystic Fibrosis.[6]
However, due to the lack of regulation on the matter, CRISPR has also been used irresponsibly. For example, in 2018 He Jainku edited human embryos, two of which were brought to term using in vitro fertilization.[7] He tried to make a genetic edit which would make the two embryos immune to HIV, a procedure which was reckless and unnecessary as HIV already has many effective treatments. Most importantly, according to Sheldon Krimsky he also did not "comply with the national ethical guidelines in China for embryo research" and was not punished for it.[8] All this means that it is possible to cut out or insert a gene of interest with a simple and inexpensive procedure, but the few legislative frameworks that do exist are often not enforced. Concerns about privacy and the ethics of this cutting-edge technology lead us to consider the following question: is current US regulation of germline CRISPR editing effective or should a moratorium be placed on all research in the area in the future? This paper aims to show that a moratorium would not be the most effective solution to the issue at hand, as it would prevent many crucial developments in the field. Instead this paper calls for the government for Independent Review Boards (IRBs) to be established in order to ensure the safety of the research. In addition, the current ban on government-funded embryonic research should be repealed. This will allow the US to keep up with other competing nations in the area of germline editing, while ensuring that the research conducted does not pose a risk to the nation.

Many scholars have considered the dangers of germline gene editing, though they differ in their solutions to the problem. On the one hand, Paul Enriquez, in the Vanderbilt Journal of Entertainment & Technology, praised the UK Human Fertilization and Embryology Authority (HFEA) for being the first national regulatory agency to condone research involving human germline editing in 2016.[9] He stated that this is an "important step toward elucidating more knowledge regarding CRISPR systems and their roles in genome editing," arguing that by allowing the research to happen and introducing regulations such as only allowing editing on "healthy human embryos younger than seven days" the government will actually make gene editing safer as it will allow the development of a "more rigorous and developed framework" than that of the research of He Jainku.[10]

On the other hand, Alicia Opar criticized existing global legislation in her 2019 Nature article.[11] She pointed to the fact that He Jiankui was able to genetically edit two twins in 2018 to try and disable the pathway that HIV used to infect cells, without crossing any legal line. She claimed that he did not, in fact, stray from any of the guidelines set out by a review panel in 2017.[12] Her assertion contradicts that of Sheldon Krisky who stated that He Jainku did not "comply with the

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6 Paul Enriquez, "Genome Editing and the Jurisprudence of Scientific Empiricism," *Vanderbilt Journal of Entertainment and Technology Law* 19, no. 3 (Spring 2017): Page 668, Ncbi.

7 Sheldon Krimsky, "Ten Ways in Which He Jiankui Violated Ethics," *Nature Biotechnology* 37 (2019): https://www.nature.com/articles/nbt.4337.

8 Krimsky, 2019.

9 Enriquez, 2017.

10 Enriquez, 2017.

11 Alisa Opar, "CRISPR-edited Babies Arrived, and Regulators Are Sill Racing to Catch up," *Nature Medicine* 25 (November 2019): Page 1634, Ncbi.

12 Opar, 2019.

national ethical guidelines in China for embryo research."[13] However, both scholars agree that he was not punished for it and this shows that there are still significant gaps in either the legislation or its enforcement. Opar suggested that the US should lead with instituting a binding global moratorium on germline genome editing until more research has been done.[14]

One of the most common arguments against germline CRISPR editing is that allowing embryonic cells to be edited will lead to the creation of designer babies with superior intelligence and athletic ability. Mary Todd Bergman of *The Harvard Gazette* supports this view and stated that people view germline CRISPR editing as a way "for the privileged to vault ahead."[15] This view presents a dire perspective on CRISPR as it suggests that in the future doctors will be able to "dictate traits such as the gender, height, or intelligence of their baby," naturally posing issues of inequality between the wealthy and the poor.[16] Kashyap Vyas also suggested that those who can afford gene editing will be given an "advantage" and such a divide in affordability will lead to a "genetic class system" and "allow science and not nature to guide the evolution of the human race."[17] This argument suggests that such a dangerous possibility can only be prevented by the institution of a moratorium of germline genome editing in the US. This also appears to be the view shared by Feng Zhang, one of the inventors of CRISPR, when he issued a statement the day after He Jainku claimed to have modified the CCR5 gene in the two embryos to make them resistant to HIV.[18] Zhang stated that "the risks of editing embryos to knock out CCR5 seem to outweigh the potential benefits."[19] Aside from calling the experiment irresponsible, Zang also stated that "given the current state of the technology" he is "in favor of a moratorium on implantation of edited embryos."[20] However Zang also mentioned that the moratorium should in fact be a "pause" until "we have come up with a thoughtful set of safety requirements."[21] This statement suggests that Zang does not share the view that a divided society will be created, but that he thinks more effective legislation should be enforced to ensure safety.

In fact, the possibility of making a super intelligent human is not possible in the near future. According to Stephen Latham of Yale University, "there is no single gene that codes for intelligence" and thus such developments are not "currently possible in modern science," meaning that there is no need for "legislation to prevent it."[22] In fact, a 2017 paper published in *Nature* found that there are 22 genes associated with intelligence and not just one.[23] The study

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13 Krimsky, 2019.
14 Opar, 2019.
15 Mary Todd Bergman, "Harvard Researchers, Others Share Their Views on Key Issues in the Field," *The Harvard Gazette*, January 9, 2019, Page 1.
16 Kashyap Vyas, "Designer Babies: Gene-Editing and the Controversial Use of CRISPR," *Interesting Engineering*, July 4, 2019.
17 Vyas, 2019.
18 Antonio Regalado, "CRISPR Inventor Feng Zhang Calls for Moratorium on Gene-edited Babies," *MIT Technology Review*, November 26, 2018, Page 1, accessed April 29, 2020.
19 Regalado, 2018.
20 Regalado, 2018.
21 Regalado, 2018.
22 Stephen Latham, "CRISPR, Will It Be Dangerous in the Future?" (lecture transcript, Yale University, Maison Mathis, CT, February 19, 2020).
23 Suzanne Sniekers et al., "Genome-wide Association Meta-analysis of 78,308 Individuals Identifies New Loci and Genes Influencing Human Intelligence," *Nature* 49, no. 7 (July 2017), Nature.

analyzed 78,308 individuals and identified 336 associated single nucleotide polymorphisms (small genomic fragments), and placed them in 18 loci in 22 genes.[24] It is important to note that 11 of these genes had not been previously identified which demonstrated the rapid development and increasing complexity of the study of genetic intelligence. The fact that there are 22 genes currently known that are linked to intelligence shows that a single nucleotide CRISPR edit will not be able to render someone a genius. Additionally, many of the genes discovered were responsible for regulating cell development pathways.[25] This means that even if there was a single loci (place on the gene) that was discovered the CRISPR edit could have cascading effects in the cell development pathways which would make the experiments very unpredictable and dangerous. Another study, accomplished just a year later, showed that there were in fact 538 genes implicated.[26] Of course, many of these genes have a minute effect on intelligence; however, they still play a role. All this shows that current research in the field is still finding new genes linked to intelligence at a very rapid pace and thus we are not going to be able to create super intelligent humans with CRISPR in the near future, rendering the idea of a worldwide moratorium for this reason illogical.

In addition to this, there is little support for the theory that a human with superior athletic abilities can be created using CRISPR germline editing. To date, there are two genes which are associated with athletic performance: ACTN3 and ACE.[27] The ACTN3 gene provides instruction for making the protein called alpha (α)-actinin-3 which is associated with fast twitch muscle fibers and ACE helps the synthesis of the angiotensin-converting enzyme.[28] The enzyme converts angiotensin I to angiotensin II which helps to control blood pressure. ACE may also influence skeletal muscle function, however its role is not completely understood.[29] Though these genes have been identified to have an association with athletic performance,researchers in the field disagree about their significance. A 2016 study by Ioannis Papadimitriou et al., though their analysis of sprint time and genotype, found that the percent "sprint time variance explained by ACE and ACTN3 is substantial at the elite level and might be the difference between a world record and only making the final."[30] In contrast, a study in the same year by Ahmetov et al. in the journal of Medicine and Sport Science, found that there are 155 genetic markers which are linked to elite athlete status.[31] They found 93 endurance related genetic markers and 62 markers related with power and strength, thus showing that instead of one single gene which codes for athletic prowess the genetic landscape is complicated. This disagreement in the field shows that so far scientists have not identified a single gene which regulates athletic success and even if a gene such as ACTN3 and ACE was able to be altered by CRISPR in an embryo, the possible side effects of such a procedure would be too dangerous to make it feasible. This shows that the implementation of a worldwide moratorium on CRISPR germline gene editing is not necessary,

[24] Suzanne Sniekers et al. 2017.
[25] Suzanne Sniekers et al. 2017.
[26] W. D. Hill et al., "A Combined Analysis of Genetically Correlated Traits Identifies 187 Loci and a Role for Neurogenesis and Myelination in Intelligence," *Molecular Psychiatry* 24 (2019): Page 169.
[27] U.S. National Library of Medicine, *Is Athletic Performance Determined by Genetics?* 2020.
[28] U.S National Library of Medicine 2020.
[29] U.S National Library of Medicine 2020.
[30] Ioannis D. Papadimitriou et al., "ACTN3 R577X and ACE I/D Gene Variants Influence Performance in Elite Sprinters: A Multi-Cohort Study," *BMC Genomics* 17 (April 13, 2016), NIH.
[31] Ildus I. Ahmetov et al., "Genes and Athletic Performance: An Update," *Medicine and Sport Science* 61 (June 10, 2016).

as the complicated genetic factors which influence athletic ability make the creation of super humans highly unlikely. Instead, more focus should be placed on legislation which prevents such dangerous editing as it can introduce lots of dangerous mutations into the gene pool.[32]

Another reason why a worldwide germline CRISPR editing moratorium would not be the best solution is the fact that CRISPR embryo editing can provide numerous treatments of existing conditions such as Sickle Cell Disease. Richard Hamershesh, the faculty co-chair of the Harvard Business School and the Kraft Precision Medicine Accelerator stated that there is "no question that gene editing technologies are potentially transformative and are the ultimate precision medicine."[33] He further supplemented this by stating that if you could precisely "correct or delete genes that are causing problems" it would be very "transformative for people with diseases caused by a single gene mutation, like sickle cell anemia."[34] This is in fact a very powerful argument as a single CRISPR edit in a genetic embryo could prevent a child from having a crippling and potentially debilitating disease. This theory is supported by a paper by Mark Dewitt et al., which in 2016 showed the potential of treating Sickle Cell Disease (SCD) with CRISPR.[35] In the paper the researchers optimized the delivery of a ribonucleoprotein (RNP) which is a complex consisting of the Cas9 protein and an unmodified single guide RNA, together with a single-stranded DNA oligonucleotide donor (ssODN).[36] This enabled them to replace the Sickle Cell mutation in human CD34+ hematopoietic stem/progenitor cells (HSPCs). The corrected HSPCs were then implanted into immunocompromised mice, where they maintained the SCD gene edits for 16 weeks at a level "likely to have clinical benefit."[37] This paper provides a clinical basis for treating Sickle Cell Disease and other hematopoietic diseases using the CRISPR-Cas9 technology. A U.S. moratorium would mean that research into a disease that affects approximately 90,000 people in the U.S. would be discontinued in terms of human germline editing.[38] Therefore even if a clinical solution in early pregnancy could be possible it would not be allowed to be implemented. All this calls for more comprehensive regulation on CRISPR germline editing to be developed instead of the cessation of all research in the field.

Furthermore, a paper published in 2018 by Michele Marangi and Giuseppa Pistritto proposed that CRISPR could be used to make germline edits in order to prevent cystic fibrosis.[39]Cystic Fibrosis (CF) is one of the most common lethal genetic diseases and it is caused by mutations in the CFTR gene. Though various treatments have improved life expectancy, there is still no cure for the disease. Marangi and Pistritto have suggested that it could be possible to correct the CFTR mutation, though no studies on humans have been done to date. They also suggest that CRISPR can be used for personalized therapy as CF is caused by a "constellation of mutations", but CRISPR will allow for the treatment to be "readily tailored" to target an "individual patient's

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32 U.S. National Library of Medicine 2020.

33 Bergman 2019.

34 Bergman 2019.

35 Mark A. DeWitt et al., "Selection-free Genome Editing of the Sickle Mutation in Human Adult Hematopoietic Stem/Progenitor Cells," *Science Translational Medicine* 8, no. 360 (October 12, 2016).

36 DeWitt et al. 2016.

37 DeWitt et al. 2016.

38 Jean-Antoine Ribeil et al., "Gene Therapy in a Patient with Sickle Cell Disease," *The New England Journal of Medicine* 376 (March 2, 2017).

39 Michele Marangi and Giuseppa Pistritto, "Innovative Therapeutic Strategies for Cystic Fibrosis: Moving Forward to CRISPR Technique," *Frontiers in Pharmacology* 9, no. 396 (April 20, 2018).

mutations."[40] Though this research seems promising, it is important to note that this paper is merely theoretical, however if such a treatment is possible it will be revolutionary for those who want to ensure their children are not affected by the disease. Richard Hamermesh has also commented on the benefits of germline editing to alleviate cystic fibrosis. He stated that the development of safe and "effective ways to use gene editing to treat people with serious diseases with no known cures has so much potential to relieve suffering that it is hard to see how anyone could be against it."[41] All this shows CRISPR germline editing to be an indispensable tool for treating diseases such as sickle cell and cystic fibrosis, as opposed to a scary technology which will create designer babies. Thus the aforementioned research shows that the establishment of a worldwide moratorium on germline CRISPR editing will cease the progression in fields where little success has been achieved with other technologies. Such a choice would not be justified given the 30,000 people who have CF in the US as well as the 90,000 people who have Sickle Cell anemia in the US.[42]

Another reason why a worldwide moratorium should not be placed on CRISPR germline gene editing is because sufficient legislation is already in place for CRISPR editing in adults in the U.S. and thus similar legislation can be adapted and implemented for germline editing. Currently, Title 45 of the Code of Federal Regulations, Subtitle A, Subchapter A, Section 46 details the laws in existence for the protection of human subjects.[43] Section §46.101 establishes that this "policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research" it also includes research "conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States."[44] This means that almost any research carried out on adult and child human tests subjects in the United States has to be reviewed by an Institutional Review Board (IRB). An institutional review board is tasked with assessing whether a research plan minimizes the risks to participants, ensuring that the risks to participants are reasonable in relation to anticipated benefits, the selection of subjects is equitable, that informed consent is sought, that the data is collected safely and that the privacy of the subjects is prioritized to maintain confidentiality.[45] The review board has to consist of at least five members "with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution."[46] In practice this means that each IRB should have at least one member "whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas," as well as one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution."[47] No member who has a conflicting interest can participate in the initial or continuing review of any project conducted by an IRB.[48] Such a comprehensive and detailed rule ensures that the research

[40] Marangi and Pistritto 2018.
[41] Bergman 2019.
[42] Ribeil et al. 2017.
[43] Public Welfare, 45 C.F.R. § Part 46.101 (2019) (eCFR, Subtitle A, Subchapter A, Part 46).
[44] Public Welfare, 45 C.F.R. § Part 46.101 (2019).
[45] Public Welfare, 45 C.F.R. § Part 46.111 (2019).
[46] Public Welfare, 45 C.F.R. § Part 46.107 (2019).
[47] Public Welfare, 45 C.F.R. § Part 46.107 (2019).
[48] Latham 2020.

conducted is reviewed by a group of qualified and objective personnel. It also ensures that the research study continues to be reviewed yearly, or more frequently than annually if the respective IRB decides to do so. This demonstrates that, in the United States, adult CRISPR editing is well regulated on the macroscopic level. It is important to note, however, that Title 45 does not include a section on germline gene editing or germline research of any kind.[49] All this illustrates that there is sufficient, comprehensive legislation already in place in the United States that ensures the safety of the research in human adult subjects, thus setting a precedent for the creation of similar legislation for germline gene editing. If institutional review boards can be established for the regulation of germline CRISPR editing then they will be as comprehensive as the current U.S. legislation and thus a moratorium on germline gene editing would be unnecessary, as it would ignore the benefits (aforementioned) that germline gene editing could provide.

Consequently, the establishment of Institutional Review Boards and other review bodies, would allow germline gene editing to proceed safely and effectively, showing that a moratorium in the US would not be the best position. Stephen Lathan, a professor at Yale University is in favor of the establishment of IRBs to review germline gene editing expremients. He is currently the chair of Yale's Human Subjects Committee (the social and behavioral IRB) and the co-chair of Yale's Embryonic Stem Cell Research Oversight Committee. In a recent interview he stated that he supports the institution of germline gene editing IRBs and believes they will have an "instrumental" role in changing the landscape of the safety of germline gene editing.[50] IRBs are comprehensive, objective and oriented at ensuring the safety of the research subjects. The establishment of IRBs in the area of germline gene editing will ensure that research conducted in the field is rigorously reviewed prior to being allowed to proceed, and then monitored and reviewed yearly once it has begun.[51] In addition to the creation of IRBs in CRISPR genome editing, research in this field will also crossover with review by Embryonic Stem Cell Research Oversight (ESCRO) committees, as their task is to provide oversight on issues related to the derivation and use of hESC lines.[52] ESCRO reviews protocols and approves of the scientific merit of the research conducted in human embryonic stem cells.[53] A lot of the research in the germline which uses CRISPR will be done in embryonic stem cells and thus it will have to be reviewed by ESCRO. This means that if IRBs in the germline editing field are established, then there will be two independent review organizations which will ensure the safety of the research in the US. These are exactly the kind of "thoughtful set of safety requirements" that Feng Zang mentioned in his statement following Hee Jainku's reckless use of CRISPR in 2018.[54] Therefore, with such robust checks in place it would be logical to not implement a moratorium in germline gene editing in the US.

[49] Latham 2020.
[50] Latham 2020.
[51] Public Welfare, 45 C.F.R. § Part 46.107 (2019).
[52] Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (Washington, DC: National Academies Press, 2010), digital file.
[53] Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee 2010.
[54] Regalado 2018.

Finally, if a moratorium on germline gene editing is placed in the US, other countries such the Russian Federation will get ahead. Currently in the US the NIH cannot fund any research in which an embryo's germline is edited and the FDA cannot consider clinical trial applications for any human germline genome editing.[55] It is important to note, however, that in some states non-clinical research is legal but it must be funded by non-federal sources.[56] Though there are limitations in the US the rules are not as clear as in other countries. For example the Russian Federation has a "law that prohibits genetic engineering under most circumstances", however it is "unclear how the rules would be enforced with regard to gene-edited embryos."[57] Such lax regulation has led to Denis Rebrikov, a Russian molecular biologist to seek funding and approval from three government agencies for his experiments to create HIV-protected babies, in spite of the outrage with He Jainku's experiments.[58] He is currently waiting for the approval of the Ministry of Health of the Russian Federation. Konstantin Severinov, who is a tenured professor at Rutgers University and also works at Skolkovo Research Institute stated that "In Russia, it would be unlikely that all scientists would listen to whatever US, or US-backed, scientists have to say."[59] This statement supports the idea that if the US institutes a moratorium that other countries will not follow suit and will instead use this as an opportunity to forge ahead. Jennifer Doudna, another one of CRISPR's inventors at the University of California Berkeley stated that though she called for a worldwide moratorium in 2015 she no longer supported the idea as she believes the time for such a motion has passed. Instead, she suggested: "We have to put in place international requirements and consequences to crossing the line with those requirements, ensuring that we don't see premature use of human germ-line editing in the near future."[60] In another interview she also stated that now the "word 'moratorium' implies that you're not going to proceed to discuss the topic."[61] All this shows that the most effective way for the US to proceed is not to institute a moratorium, as it will not be followed by other countries. Instead the US should move to set a precedent in regulation and management, while also maintaining their leading position on CRISPR research in the world.

Overall, the current US regulation of general CRISPR editing is well managed by IRBs; however, this legislation is not extended to germline genome CRISPR editing. Despite the assertions of some, genome CRISPR editing will not lead to the creation of designer babies with superior intelligence or athletic abilities as both of these traits are affected by a multitude of genes and the editing of one would not lead to a guaranteed significant change. On the contrary, CRISPR genome editing has the potential to act as a cure for debilitating diseases such as cystic fibrosis or sickle cell disease and thus a moratorium on research would prevent the development of those treatments. More importantly ESCRO is a review board which is already in place to regulate embryonic stem cell research which means that a moratorium would invalidate a lot of the research which has already been approved. If a moratorium is established then other countries such as the Russian Federation will use this as an opportunity to continue with

[55] Opar, 2019.
[56] Opar, 2019.
[57] Opar, 2019.
[58] Opar, 2019.
[59] Opar, 2019.
[60] Karen Weintraub, "Scientists Call for a Moratorium on Editing Inherited Genes," *Scientific American*, March 13, 2019, The Sciences.
[61] Opar, 2019.

germline research thus continuing the dangerous studies. Instead, the US should establish IRBs to regulate the germline genome research. The continuation of CRISPR germline research is crucial as the establishment of a moratorium would set a precedent for stopping the discussion and shying away from the difficult ethical questions, a precedent which could be carried further into other emerging technologies. Instead, we should focus on ensuring the legislation which facilitates this cutting edge research is strong and the repercussions for violations are severe.

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