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The Widespread Ethical Disagreement of CRISPR-Cas9

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ABSTRACT

In the early 21st century, gene therapy, specifically CRISPR-Cas9, was developed as a viable option to prevent heritable diseases and treat genetic disorders in somatic and germline cells. However, the advancement of this technology has led to misuse, as genetic "engineers" aim to alter the DNA of future generations to conform to an idealistic set of standards. The abuse of technology, coupled with the ability to reconstruct an individual's genetic makeup, leads to the societal question about the best way to regulate this software. This paper addresses three key factors in preventing misuse while maximizing medical benefits: the public's role, physician-patient relationships, and diversity in healthcare. This paper analyzes how the public should engage with national organizations and participate in formal discussions to express their views regarding CRISPR-Cas9 governance; without explicit expression of their views, their beliefs will likely be undermined by professionals. Furthermore, this paper emphasizes transparency and communication within physician-patient relationships: physicians must offer the comprehensive health benefits and drawbacks of gene editing to ensure patients considering gene editing operations are aware of its implications. Additionally, this paper asserts the need to bridge the socioeconomic gap within healthcare to extend access to gene editing to a larger group and also gain deeper insight into CRISPR-Cas9's long-term impacts on people of various backgrounds. This paper states that the resolution of these three components is essential to reach a societal consensus of the appropriate regulations on gene editing, thereby halting the temporary ban on the technology.

Introduction to CRISPR-Cas9

Developed in 2012, CRISPR-Cas9 is a modern genome technology able to target and modify specific genes within one's body. Since then, this advancement has evolved and more than 200 people have undergone gene editing operations, illustrating the increasing widespread influence of the innovation (Hamzelou, 2023). However, CRISPR-Cas9 has received enormous controversy from medical professionals, geneticists, and national organizations regarding its ethics in germline gene editing, where genetic modifications are transmitted to future generations. The lack of knowledge regarding CRISPR's long-term effects, the misuse of the technology by various scientists (such as He Jiankui, who used CRISPR to alter the genome of the embryos of twin girls, in order to produce HIV resistance), and the unsafe, unapproved methods that patients use for genetic editing results in the exacerbation of this debate. In 2019, an international group of 18 scientists, including CRISPR developers Feng Zhang and Emmanuelle Charpentier, along with Nobel Prize recipient Paul Berg, signed a *Nature* commentary calling for a moratorium on the technology to ensure it is not used dangerously (Kaan et. al, 2021). However, this moratorium has received enormous backlash, with many scientists, institutions, and entire nations continuing to operate this gene editing software. The lack of consensus amongst society results in an inability to use the nascent technology properly and effectively for overall public health improvement. While the general health of society could be vastly improved by this revolutionary software, the constant quarrel regarding the ethics of the technology prohibits the advancement of contemporary medicine. The question

arises: to what extent should CRISPR-Cas9 be implemented into germline gene editing? However, before discovering an answer, we must address various factors.

Moral Ambiguity of CRISPR-Cas9

However, some argue that the unrestricted incorporation of CRISPR-Cas9 into the medical setting will stunt the growth of healthcare, as a whole. Conversely, others believe that it is a revolutionary technology that will transform humanity in the prevention of dangerous diseases and illnesses. The CRISPR-Cas9 technology possesses the unique ability to delete or transform genes within one's body, some of which can be passed on to future generations. Germline cells (often referred to as the "reproductive cells") consist of the sperm and egg cells, and any modifications made to these cells would consequently affect the offspring of the individual. Conversely, somatic cells are not involved in the reproductive abilities of a human, causing there to be relatively minimal debate regarding the use of CRISPR-Cas9 on somatic cells.

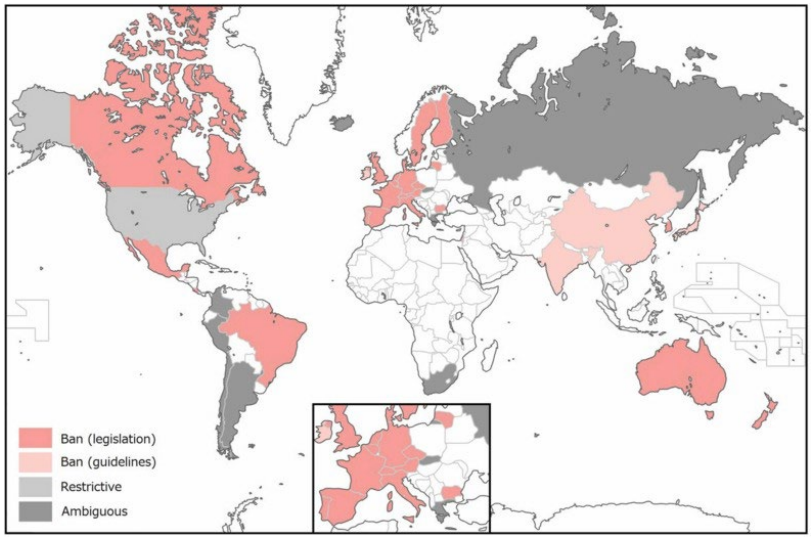

Figure 1. International landscape of human germline gene regulation (Araki & Ishii, 2022)

CRISPR-Cas9 contains the Cas9 enzyme, which acts as a genetic "scissors". The enzyme is able to separate the two strands of DNA at a specified location, thus allowing genes to be added, altered, or deleted. The CRISPR-Cas9 technology also consists of a form of RNA called guide RNA (abbreviated gRNA). The gRNA sequence binds to a predetermined sequence within the DNA, matching corresponding bases with each other. Meanwhile, a smaller strand within the gRNA guides the Cas9 enzyme (mentioned earlier) to the specified sequence within the DNA strand that the technology aims to rectify.

However, the editing process of this technology constitutes many new questions regarding the use of CRISPR-Cas9 in breeding. For instance, genome editing can lead to the alteration of physical attributes that have no significant impact on one's health level, such as skin color. For instance, in one study testing the implications of CRISPR-Cas9 on rats, the color of the rodents' fur was altered by this technology (Yoshimi et al. 2014). Additionally, Chinese scientist He Jiankui performed the first human gene editing on germline cells, by modifying the CCR5 gene in embryos, in an attempt to increase HIV resistance in the cells of twin girls (Alsaigh et al. 2019). However, his operation led to extreme controversy when it was revealed that the embryos had no prior significant risk of developing HIV, indicating that his use of CRISPR-Cas9 was uncalled for and posed a grave danger to society. Furthermore, Dr. Josiah Zayner demonstrates a clear abuse of his medical title when

he self-injected CRISPR into his forearm to strengthen and modify his muscle cells (Regalado 2019). Owner of a widespread genetic engineering company "The Odin", Zayner's experience clearly implies the threat of CRISPR-Cas9 to society: as more and more individuals are able to gain access to this technology, they are likely to become influenced to use it inappropriately and devoid of any guidelines or professional assistance. The misuse and lack of regulations reveals the reasoning behind public disapproval of CRISPR-Cas9, as well as the dire need for a set of requirements to guide the use of this technology and ensure it is only operated in a medical setting under the surveillance of trained, vetted professionals.

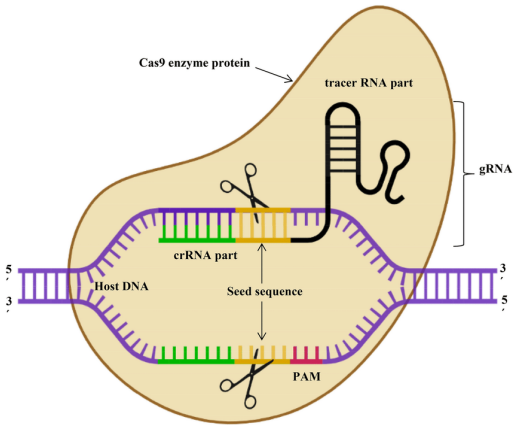

Figure 2. CRISPR-Cas9 activation in the genome (Kashtwari et al. 2022)

Public's Role in CRISPR's Ethics Consideration

One such group that convened to resolve this ethical controversy, the German Ethics Council, focused on the holistic impact of gene editing, rather than simply the medical aspect of the technology, illustrating how they adopted a common viewpoint of society (instead of only the health professionals) when considering CRISPR's ethics (Schweikart, 2019). Rather than simply viewing CRISPR-Cas9 from an analytical cost-benefit perspective, the German Ethics Council accounted for the values of dignity, trust, and responsibility in its discussion, ensuring that the regulations would not merely be confined to the field of healthcare, but rather, encompassed all the factors that accompany this technology's use. This strategy not only led to a more unified approach and solution of a moratorium, but it also contributed to widespread acceptance of their decision, as individuals of varying professions and backgrounds felt that their views were being accounted for.

Various national organizations also continue to prioritize the opinions of both scientists and the public when considering the guidelines of the new genome editing software. In fact, the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM) produced a 2017 report called "Human Genome Editing: Science, Ethics, and Governance", promoting a set of recommendations on how to engage the public in gene editing governance (Blasimme, 2019). Establishing the importance of "achieving consensus around overarching ethical principles", the NASEM reinforces the need for the involvement of society when determining the regulations of CRISPR-Cas9 technology, as the public can provide valuable insight regarding its ethical limitations (p.30).

Additionally, the 1975 Asilomar Conference, which failed to reach an agreement on the use of recombinant DNA technology, illustrates how self-regulated governances are often ineffective in evaluating the complete potential of a biotechnology, as experts may undervalue the importance of ethics in an effort to maximize the safety and harm containment of the technology (Blasimme, 2019). By collaborating with a diverse group of individuals to reach a common consensus regarding the governance of CRISPR, the public will not only ensure

that the views of all individuals are represented in their established set of regulations, but also account for any inaccuracies or fallacies within their solution.

Physician-Patient Relationships

Physicians also hold a major role in CRISPR's implementation: As direct caretakers of society, physicians are responsible for effectively communicating genetic editing information to their patients, in order to prevent the use of unauthorized medical software. The American Medical Association (AMA), the leading group of professional medical physicians in the United States, supports the implementation of CRISPR, but only if specific governance and regulations are established. In fact, Lisa Lehmann of the AMA set forth the notion of the 4-S Framework, a model that physicians can institute when patients are interested in undergoing gene editing software. In this model, the doctor must elaborate on CRISPR's safety and the uncertainty of its risks, establish the significance to which harm can be prevented, inform the patient on the unknown consequences of CRISPR on offspring and future generations, and discuss the social consequences of CRISPR (Lehmann, 2019). With an overwhelming increase in unapproved gene editing technologies in recent years, physicians have an immediate duty to foster health literacy and spread knowledge of CRISPR. Only with this knowledge will society be equipped to adequately determine the use of CRISPR-Cas9.

However, the responsibilities of physicians encompass much more than the mere spread of knowledge. If germline editing has been conducted, physicians are responsible for monitoring the lives of the babies, to discern the long-term consequences. Charis Thompson (2019), a researcher part of the AMA, describes the importance of routinely collecting the physiological data of genetically edited children and comparing it to the information of non-gene edited children receiving the same medical care, which would better illustrate the implications of CRISPR in the real world. Furthermore, Thompson (2019) describes how various physicians should monitor the child's milestones and review their mental health to ensure the child's knowledge of the CRISPR procedure does not affect their overall independence and trust in medical professionals. The current inability to answer certain health-related questions about CRISPR reveals the overwhelming need to monitor patients who have experienced gene editing. By observing CRISPR-edited babies, clinicians can collect data about the impacts of gene editing and be more equipped to establish policies/advancements to better regulate an appropriate use of the technology.

Diversity and Inclusion

Moreover, uncertainty about the effects of CRISPR on various groups and demographics has intensified the hesitation surrounding its applicability. The lack of diversity in genomic research leads to the inability to create therapies specifically to address the genomic makeup of minority populations. Various factors also contribute to the low current enrollment rates of minority groups in studies, with less than 4% of participants in genome-wide association studies being of African, Latin American, or native descent (Fullerton & Popejoy, 2016). The perpetual mistreatment of minority groups, prioritizing the acquisition of knowledge over advancing the health of these humans, has discouraged many individuals from participating in medical studies, as they feel their well-being will be undermined by researchers. Furthermore, minority groups' lack of accessibility to different forms of treatment contributes to their perceived futility of engaging in medical studies, as they believe the research will not produce any healthcare benefits for them. The low representation of minority groups in research prevents scientists from learning about links between genetic variants and disease within populations. Furthermore, the lack of representation in clinical trials has effects far greater than a mere stunt in education. For instance, in a clinical trial of Crenezumab, a drug to treat Alzheimer's, only 2.8% of participants were Hispanic, despite the fact that their likelihood of being diagnosed with the disease is 1.5 times that of white

individuals (Armstrong 2022). Correspondingly, in the phase 3 clinical trial of Ninlaro, a drug prescribed to treat multiple myeloma, the proportion of Black participants was a meager 1.8%, although the presence of the disease is statistically higher in African Americans (Sharma & Palaniappan 2021). The direct lack of representation within clinical trials reveals the necessity to include all groups and ethnicities in studies testing the effectiveness of CRISPR-Cas9. By limiting access to the technology or restricting the subjects in medical studies to a select few, society will hinder the growth of CRISPR-Cas9, since we will not only be unable to discern its true effects on a wide group of individuals, but we may inadvertently limit the treatment to a predetermined few, even if a minority group urgently requires the technology. In addition, the strong correlation between race/ethnicity and socioeconomic status exacerbates the inability to provide gene therapy to minority groups due to financial burdens, further reducing access to gene treatments for minority populations.

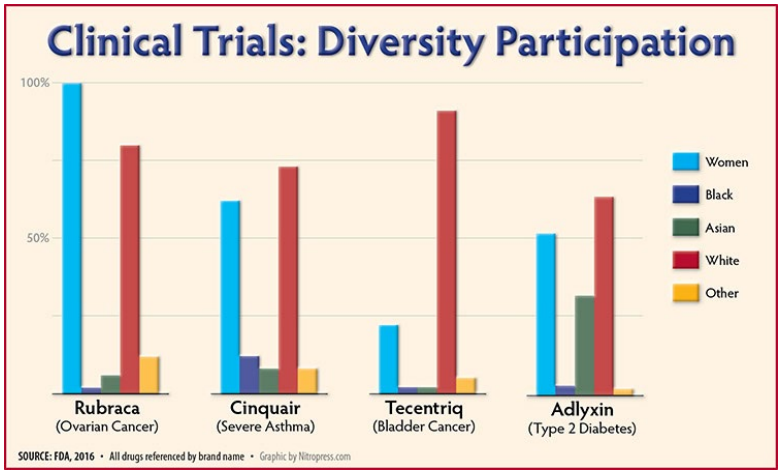

Figure 3. A graph depicting the participation of diverse groups in various clinical trials (Srinivasan 2017)

However, the Human Genome Diversity Project and the National Institute of Health (NIH) All of Us research project have been successful attempts to address the lack of diversity in research (Hildebrandt & Marron, 2018). By increasing the diversity of genomic databases, scientists can not only view more relevant, specific research, but society can also benefit from the increased trust and risk-taking abilities of minority communities. In fact, the National Human Genome Research Institute signifies how certain organizations already have groups dedicated to researching the genomic health disparities amongst minority groups, which can further increase transparency, justice, and access (Hildebrandt & Marron, 2018). The rise in equitable healthcare will result in more specialized knowledge regarding the effects of CRISPR on a multitude of individuals, contributing to a more nuanced view of its ethical implications. Hence, research organizations and scientists should establish large-scale data-collecting methods and reduce the social gap in CRISPR trials to increase knowledge about the technology, specifically its long-term effects on both the embryos and the patients.

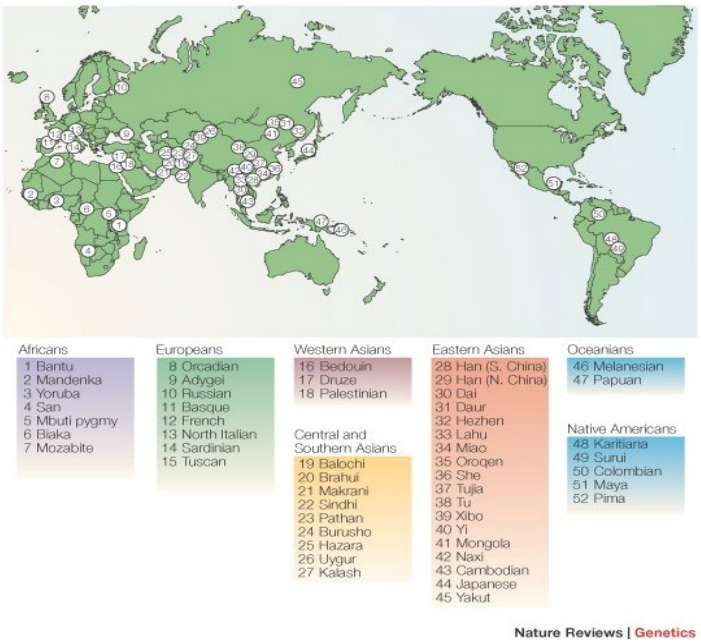

Figure 3. Populations Included in the Human Genome Diversity Project (Cavalli-Sforza 2005)

Societal Approach

When determining the appropriate parameters within which CRISPR should abide by, society must consider various perspectives that people hold about CRISPR's use. While the potential risks/effects of CRISPR may contribute to one's wariness of the technology, the innovation's revolutionary benefits may thrill others. Whether it be medical professionals, researchers, health organizations, or simply the general public, when establishing a set of guidelines to govern the use of CRISPR, each group's fundamental opinions and beliefs must be incorporated. In order to reach a common consensus regarding the appropriate use of CRISPR, we must form a solution that includes the views of all groups, while ensuring we are up to date on the most recent information about the technology. It is only then that society will be able to maximize use of this revolutionary advancement. With a technology that is equipped to reduce the spread of deadly diseases by animal vectors, treat genetic disorders, engineer crops to boost agricultural yields, and prevent the progression of cancer, it is essential that we find an acceptable balance to govern the use of CRISPR-Cas9.

Conclusion

With the increasing need of a technology in healthcare that can safely counteract diseases like cancer and sickle-cell disease, CRISPR-Cas9 can offer a wide range of benefits to its patients. However, there are drawbacks about the power of CRISPR-Cas9 that need to be considered, as well. For instance, the recent development of "designer babies"- a phenomena in which parents select the most desirable traits for their offspring- directly opposes the laws of nature. In order to ensure that CRISPR-Cas9 is used in a responsible manner, the general public must engage in formal discussions regarding the appropriate governance of the technology. Additionally, physicians must promote transparency and establish clear communication and education within their physician-patient relationships, to prevent misuse and uninformed decision to undergo the gene editing operation. Lastly, inclusion must be implemented into the CRISPR-Cas9 procedure: all individuals should be exposed to equal access to this technology, instead of research studies limiting their experimental subjects to a subsect of the

population. We suggest that it is only with the resolution of these three factors that CRISPR-Cas9 be implemented into healthcare operations.

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References

Alsaigh, T., Nicholson, L., & Topol, E. (2019, December 1). What should clinicians do to engage the public about gene editing?. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/what-should-clinicians-do-engage-public-about-gene-editing/2019-12

Araki, M., & Ishii, T. (2014, November 24). International regulatory landscape and integration of corrective genome editing into in vitro fertilization - reproductive biology and endocrinology. BioMed Central. https://rbej.biomedcentral.com/articles/10.1186/1477-7827-12-108

Armstrong, A. (2022, May 18). “we just don’t have the studies”: New report details critical diversity shortcomings in US clinical research. Fierce Biotech. https://www.fiercebiotech.com/biotech/we-just-dont-have-studies-new-report-details-critical-diversity-shortcomings-us-clinical

Asmamaw, M., & Zawdie, B. (2021). Mechanism and Applications of CRISPR/Cas-9-Mediated Genome Editing. Biologics : targets & therapy, 15, 353–361. https://doi.org/10.2147/BTT.S326422

Ayanoğlu, F. B., Elçin, A. E., & Elçin, Y. M. (2020). Bioethical issues in genome editing by CRISPR-Cas9 technology. Turkish Journal of Biology, 44(2), 110–120. https://doi.org/10.3906/biy-1912-52

Balch, B. (2021a, December 2). The future of CRISPR is now. AAMC. https://www.aamc.org/news/future-crispr-now

Baylis, F. (2018). Counterpoint: the potential harms of human gene editing using CRISPR-CAS9. Clinical Chemistry, 64(3), 489–491. https://doi.org/10.1373/clinchem.2017.278317

Blasimme, A. (2019, December 1). *Why include the public in genome editing governance deliberation?*. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/why-include-public-genome-editing-governance-deliberation/2019-12

Chapman, C. R., & Caplan, A. L. (2019, December 1). How should physicians respond when they learn patients are using unapproved gene editing interventions?. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/how-should-physicians-respond-when-they-learn-patients-are-using-unapproved-gene-editing/2019-12

El-Galaly, T. C., Gaidzik, V. I., Gaman, M. A., Antic, D., Okosun, J., Copland, M., Sexl, V., Fielding, A. K., Doeswijk, R., Parker, H., Dreyling, M., Döhner, K., Almeida, A. M., Macintyre, E., Gribben, J. G., & Grønbæk, K. (2023). A Lack of Diversity, Equity, and Inclusion in Clinical Research Has Direct Impact on Patient Care. HemaSphere, 7(3), e842. https://doi.org/10.1097/HS9.0000000000000842

Graham, D. B., & Root, D. E. (2015, November 27). Resources for the design of CRISPR gene editing experiments - genome biology. SpringerLink. https://link.springer.com/article/10.1186/s13059-015-0823-x

Greely H. T. (2019). CRISPR'd babies: human germline genome editing in the 'He Jiankui affair'. Journal of law and the biosciences, 6(1), 111–183. https://doi.org/10.1093/jlb/lsz010

Halme, D. G., & Kessler, D. A. (2006). FDA regulation of stem-cell–based therapies. New England Journal of Medicine, 355(16), 1730–1735. https://doi.org/10.1056/nejmhpr063086

Hamzelou, J. (2023, March 10). *More than 200 people have been treated with experimental CRISPR therapies*. MIT Technology Review. https://www.technologyreview.com/2023/03/10/1069619/more-than-200-people-treated-with-experimental-crispr-therapies/

Haridy, R. (2018, July 12). Researchers discover why the CRISPR gene editing system sometimes fails. New Atlas. Retrieved October 22, 2023, from https://newatlas.com/crispr-gene-editing-what-causes-failure/55428/.

Hildebrandt, C. C., & Marron, J. M. (2018, September 1). *Justice in CRISPR/cas9 research and clinical applications*. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/justice-crisprcas9-research-and-clinical-applications/2018-09

Hirakawa, M. P., Krishnakumar, R., Timlin, J. A., Carney, J., & Butler, K. S. (2020). Gene editing and CRISPR in the clinic: current and future perspectives. Bioscience Reports, 40(4). https://doi.org/10.1042/bsr20200127

Kaan T, Xafis V, Schaefer GO, Zhu Y, Labude MK, Chadwick R (2021) Germline genome editing: Moratorium, hard law, or an informed adaptive consensus? PLoS Genet 17(9): e1009742. https://doi.org/10.1371/journal.pgen.1009742

Kashtwari, M., Mansoor, S., Wani, A. A., Najar, M. A., Deshmukh, R., Baloch, F., Abidi, I., & Zargar, S. (2022, June). Random mutagenesis in vegetatively propagated crops: Opportunities, challenges and genome editing prospects. Molecular biology reports. https://pubmed.ncbi.nlm.nih.gov/34427889/

Lehmann, L. S. (2019, December 1). Using the 4-S framework to guide conversations with patients about CRISPR. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/using-4-s-framework-guide-conversations-patients-about-crispr/2019-12

McVean, A. (2020, December 30). 40 years of human experimentation in America: The tuskegee study. Office for Science and Society. https://www.mcgill.ca/oss/article/history/40-years-human-experimentation-america-tuskegee-study

Mir, T. U. G., Wani, A. K., Akhtar, N., & Shukla, S. (2022). CRISPR/Cas9: Regulations and challenges for law enforcement to combat its dual-use. Forensic science international, 334, 111274. https://doi.org/10.1016/j.forsciint.2022.111274

National Academies of Sciences, Engineering, and Medicine. 2017. Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24623.

Popejoy, A. B., & Fullerton, S. M. (2016, October 12). *Genomics is failing on diversity*. Nature News. https://www.nature.com/articles/538161a#citeas

Schweikart, S. J. (2019, December 1). *What is prudent governance of human genome editing?*. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/what-prudent-governance-human-genome-editing/2019-12

Raposo V. L. (2019). The First Chinese Edited Babies: A Leap of Faith in Science. JBRA assisted reproduction, 23(3), 197–199. https://doi.org/10.5935/1518-0557.20190042

Regalado, A. (2020, April 2). Don't change your DNA at home, says America's first CRISPR law. MIT Technology Review. https://www.technologyreview.com/2019/08/09/65433/dont-change-your-dna-at-home-says-americas-first-crispr-law/

Scheper, A. (2019, December 1). AMA policies and code of medical ethics' opinions related to human genome editing. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/ama-policies-and-code-medical-ethics-opinions-related-human-genome-editing/2019-12

Schweikart, S. J. (2019, December 1). What is prudent governance of human genome editing?. Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/what-prudent-governance-human-genome-editing/2019-12

Sharma, A., Palaniappan, L. Improving diversity in medical research. Nat Rev Dis Primers 7, 74 (2021). https://doi.org/10.1038/s41572-021-00316-8

Srinivasan, S. (2017, June 22). Clinical trials in need of diversity. Connecticut Health Investigative Team. https://c-hit.org/2017/05/10/clinical-trials-in-need-of-diversity/

Srivastava, K., & Pandit, B. (2023). Genome-wide CRISPR screens and their applications in infectious disease. Frontiers in Genome Editing, 5. https://doi.org/10.3389/fgeed.2023.1243731

Stefanoudakis, D., Kathuria-Prakash, N., Sun, A. W., Abel, M., Drolen, C. E., Ashbaugh, C., Zhang, S., Hui, G., Tabatabaei, Y. A., Zektser, Y., Lopez, L. P., Pantuck, A., & Drakaki, A. (2023). The Potential Revolution of Cancer Treatment with CRISPR Technology. Cancers, 15(6), NA. CRISPR/Cas9: A Potential Life-Saving Tool. What's next? - PMC (nih.gov) https://link.gale.com/apps/doc/A743761463/GPS?u=j079907&sid=bookmark-GPS&xid=24d7033e

Takefman, D., & Bryan, W. (2012). The state of gene therapies: The FDA perspective. Molecular Therapy, 20(5), 877–878. https://doi.org/10.1038/mt.2012.51

Thompson, C. (2019, December 1). *How should "crispred" babies be monitored over their life course to promote health equity?* Journal of Ethics | American Medical Association. https://journalofethics.ama-assn.org/article/how-should-crispred-babies-be-monitored-over-their-life-course-promote-health-equity/2019-12

Zhang, F., Wen, Y., & Guo, X. (2014, March 20). CRISPR/Cas9 for genome editing: Progress, implications and challenges. OUP Academic. https://academic.oup.com/hmg/article/23/R1/R40/2900693