Re-imagining CRISPR: Increased Ethical and Equitable Genome Editing Regulations

Yeleung Leini Hwang

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This literature review explores the bioethical implications of CRISPR development in the U.S. with a particular focus on gene editing regulatory frameworks currently in place in the country. A total of 21 articles were analyzed with key themes including medical inequality, biohazards and biosecurity, and inadequate regulatory development. The 21 articles mostly focus on the current policies about CRISPR regulation and lists of problems of CRISPR that are being uncovered. While there are undebatable benefits of CRISPR and gene editing technology, without progressive and stringent regulation, we are likely to continue running into ethical and biological hazards. The aim of this literature review is not to connect or summarize prevailing bioethical concerns on CRISPR but to analyze the fundamental issues and point out the limits of legal policies guiding CRISPR uses in the U.S. The outcome of this literature review will allow for the ethical and beneficial development of CRISPR.

Introduction

The biomedical revolution of the early 21st century can be said to be encapsulated in CRISPR technology. Since its introduction in 2012, CRISPR, a groundbreaking genome editing technology, has revolutionized scientific research and facilitated transformative advancements in the treatment of various human, animal, and plant conditions[1]. CRISPR was first tested on humans in 2016 and the technology is still currently used for clinical trials instead of applied directly to humans(NCT02793856)[1]. Even though the trials have been successful, there is a long way to go before CRISPR is widely used and applied. In order to safely expand the usage of CRISPR, researchers and clinicians should explore regulatory shortcomings in preparation for the more widespread use of genome editing in humans.

Outside of clinical context, CRISPR is mainly used for crops and food. Primarily CRISPR allows for the modification of crops to create bigger, smaller, colorful, and more resistant plants, fruits and vegetables[2]. CRISPR also allows for the alteration of food to meet people's individual health needs; for example, CRISPR can adapt the content of gluten wheat for people with coeliac disease[3]. In addition to modification of foods, CRISPR safeguard vegetation and food supply through pest control and ecological protection. A study by Morrison et al showed that CRISPR can control invasive plants and pests by targeting and suppressing genes that are responsible for reproduction of pests, and through gene modification to prevent disease transmission between pests and the surrounding environment[3].

Among countries with genome editing capabilities, CRISPR is most highly utilized in the U.S., both in the agriculture and medical fields. While there are a multitude of genome editing regulations in the U.S., policies in the country have struggled to keep up with the fast-paced development of genome editing technology. Besides the revolutionary benefits of CRISPR in diverse areas, society should consider the unaddressed ethical and medical concerns.

Background

While the mechanisms behind CRISPR are complex and far too lengthy for me to elaborate here; in brief CRISPR is a gene editing technology that cuts DNA. Scientists use CRISPR technology to modify specific parts of the DNA in living organisms. Cas9 is a protein that acts like a molecular scissor. In order to work as a scissor and cut the right place of DNA, the guide molecule called gRNA helps Cas9 to find the correct spot in the DNA. To break the steps, the gRNA is designed by scientists aiming to guide Cas9 where to go in the DNA. In other words, gRNA is a custom-made molecule that matches the DNA sequence of the target gene that scientists want to modify. Next, gRNA pairs up with the Cas9 protein and forms a complex which is a crucial preparation for finding the target DNA. After the group of Cas9 and the gRNA move inside the cell nucleus, where the DNA resides as a long, twisted molecule that contains the genetic instructions for the cell, Cas9 and the gRNA work together to seek the exact DNA sequence they've been programmed to find. When the group(Cas9 and gRNA) finds a DNA molecule, it starts to check if the sequence of DNA matches the gRNA's sequence. Once the group finds a perfect match with the target DNA,

Cas9 works as molecular scissors. It can eventually cut both strands of the DNA at a precise location[4]. This technology keeps developing in order to broaden the usage and amplify its effects. One recent breakthrough of CRISPR technology was led by Feng Zhang at MIT and Harvard. Enabling the first programmable RNA-guided system in eukaryotes, it can be reprogrammed to edit the cells. This is efficient because it increases the efficiency and compactness used as therapeutics[5].

Results

1. Genome editing: ethics, morality, inequality, and bio-security

This section would contain the most discussed issues about CRISPR around biological and bioethical terms. They include the rights of embryos, the loss of rights of disability, discussion about medical inequality, and increasing concern about bioweapons. In the following paragraphs, I will discuss the key ethical and moral problems posed by CRISPR and consider possible solutions and policies.

Germline editing and bioethical harms

In the United States, federal funding is not provided for germline gene editing; however, there is no explicit prohibition on privately funded germline gene editing[6]. While private funding of germline gene editing is permitted, there are no clear federal guidelines and the field remains largely unregulated[7]. The usage of unregulated CRISPR for embryo editing has the potential to cause biological harm. Embryonic gene editing, such as off target, has already led to concerning outcomes such as physiological and signaling abnormalities due to the loss of functional-gene activity. Given the murky history of embryo editing, the future application and expansion of CRISPR would need to be carefully controlled and regulated[8].

Besides the concerns that arise during the process of embryo editing, there would be manipulation of the process of women donating the eggs and other bioethical issues[9]. This ambiguity creates risks and is one of the sources obscuring efficient ethical deliberation and decision making. However, many are using the technology and pushing the limits of human technology without regulation. A blanket ban on federally funded germline editing does not surpass the need for coherent and stringent regulations without which we run the risk of transgressing human rights[9]. This regulation is not a substitute for regulation if there is a loophole to continue carrying out embryo editing through private funding[6,9].

Protecting Disability rights

There are benefits of genetic modification/CRISPR techniques for individuals with genetic disabilities. Since CRISPR is very new there are concerns regarding the actual implementation and how it fits into the broader socio political sphere. Two main concerns that show up are equal allocation of CRISPR resources and continued government support of individuals with disabilities despite technological innovation. There has been advances in advocacy for people with genetic disorders, including the passage of the Americans with Disabilities Act in 1990 and the growth of both disease-specific patient advocacy groups and umbrella organizations representing large numbers of patient advocacy groups, and it is crucial to maintain this support and widen advantages to more people[10]. Not only is there national support through laws and policies, advocates for individuals with these disorders also have changed the fundamental discourse on disabilities, such as the deaf community contending that deafness is not a disability but rather a manifestation of human diversity and that it is important to protect and preserve the deaf community's culture[10]. Living with a disability in the U.S is not a reality that should be hidden, instead we should uphold the rights of people living with disability allowing them to cultivate and preserve their identities and cultures[10]. While CRISPR holds the potential to transform treatment for another of chronic diseases and disabilities, it should be applied with utmost regard for the rights of people living with disabilities[10]. In shaping CRISPR policies, we should uphold protections for disabled people and center their voices in narrative, discourse and legal changes[10].

Medical Inequality

CRISPR is a very complex technology that modifies and changes genes. If this technology is more widely used, the main users of this technology will naturally be the rich who can afford this complicated gene therapy. As the technology gets more "successful in advancing those who undergo the procedure, by definition, it is likely to result in inequality"[10]. The wealthy would easily access the technology and consequently increase the new biological inequality adding onto the current wealth inequality, which has been increasing over the past several decades and threatens social cohesion[10]. The off-target would make it more complicated regarding compensation as well. Setting up the boundary of standards to provide compensation regarding the aftermath of CRISPR would be challenging. Moreover, this minority would suffer from this technology and aftermath. Secondly, there is uncertainty of risks and benefits and making accurate predictions impossible. GMO is the most welcomed part of CRISPR, yet there are areas to concern deeply such as widened biodiversity and unexpected issues caused by outcrossing[6]. Thirdly, making perfect predictions about the process and after effects of CRISPR

is still difficult and almost impossible. Therefore, the legal frameworks for compensation and justice seeking for those affected in the future should be set up that can cover vast areas of the usage of CRISPR. Not only for the current issues about CRISPR, the society should also look further. Questions like "where can people turn to if they are failed by CRISPR?" and "what is the safety net?" would be crucial in understanding this technology. Therefore, FDA is considering most of the future and potential risks about CRISPR as both phenotypic and genotypic characterization can significantly affect safety[11]. By laying out the questions about location of unintended alteration, impact, and differences in morbidity and mortality, FDA should deeply and intensely discuss the regulation of CRISPR in order to clarify and answer these important questions[11]. For example, the unintended alterations to the composition of milk could impact the health of humans, and in particular infants.[11]

Bioweapons

Concerns about CRISPR do not stay in human genes and medical issues but they expand to the national security system[12]. By editing and modifying genes, the possibility of creating bioweapons arises. Various Congress hearings convey a sense of threat, which could justify a more restrictive stance toward the use of CRISPR technology[13]. In a hearing before the Committee on Homeland Security and Government Affairs of the US Senate in 2016, Senator Gary C. Peters expressed his concern toward new technologies such as CRISPR, which were available through fairly inexpensive kits and could be used in very negative ways,[3]

Deciding patent rights over CRISPR is highly controversial as both certain advantages and disadvantages exist simultaneously. If there is a strict patent right in CRISPR, it will obtain more strict regulations in federal perspective which would let the technology be an internationally agreed policy[13]. In contrast, disadvantages also exist. The patent rights would be the barrier to affordable healthcare that infringes upon fundamental rights, particularly related to the right of health of every person[16] This includes the lack of federal funding for CRISPR proposals, FDA endorsing clinical trials, and scientists imposing temporary bans. In order to lower the problems of these concerns, the other side of regulation should be incorporated here[16] This is very challenging to set up the regulation because this should not only cover to mitigate any potential threat but also prevent any discrimination in medical areas using CRISPR[14].

2. Current Regulatory frameworks for control, management, and use of CRISPR technology

Who regulates CRISPR in the U.S.?

Regulation of CRISPR in the U.S involves a number of different agencies with overlapping roles and priorities at times creating confusion around who is responsible for overseeing CRISPR developments. The FDA is the largest government agency enforcing and regulating CRISPR use in the country[3]. While federal funding for CRISPR application on human embryos is banned the FDA does provide regulations and recommendations for using CRISPR in human genome editing[3]. The FDA has also approved CRISPR use in agriculture and animal husbandry[15]. FDA approval and regulation for both human and agricultural use of CRISPR are currently on a scientific trial basis only[14]. It is currently unclear whether the FDA will subject CRISPR-edited crops to the same regulations as conventional genetically modified (GM) organisms[14]. In 2017, FDA began seeking public input on its regulatory policy, but it has not published new guidance for the industry on its current regulatory policy[4]. The NIH also plays a role in regulating and overseeing CRISPR applications, often with overlapping priorities with the FDA[14]. Particularly the NIH approves and funds scientific trials using CRISPR for human clinical uses; including hundreds of different diseases[6,14]. The NIH even has its own internal regulatory body concerned with gene editing technologies called the US Recombinant DNA Advisory Committee (RAC)[14]. The RAC oversees and approves proposals for CRISPR trials[14]. When creating and beginning clinical trials, privately and publicly funded research institutions such as MIT and the University of California also play a similar role to the NIH[15]. Specifically, universities have internal ethics review boards that oversee and ensure the ethical standards of CRISPR trials[16]. Privately funded institutions will also be able to create their own regulation for CRISPR applications on human embryos if the projects are privately funded[15]. Universities also include embryonic stem cell research oversight committees (ESCROs) to oversee and regulate internal research on stem cells including CRISPR applications[18]. Other organizations with less regulatory power are also key players in creating and disseminating CRISPR use recommendations[15]. These organizations include the United States National Academies of Science, Engineering, and Medicine (NASEM), the United States National Academy of Science (NAS), and the International Society for Stem Cell Research (ISSCR) among many others[17]. Overall, there are many agencies and committees that are overseeing and issuing recommendations for CRISPR use and application in clinical trial settings[18]. The regulatory landscape for CRISPR in the United States is marked by significant gaps and a lack of comprehensive oversight. Despite the existence of

numerous rules, the practical reality is that CRISPR remains largely unregulated. This is primarily due to the complex and convoluted nature of the current biotechnology regulatory regime, involving multiple federal agencies with overlapping roles. Consequently, this overlapping jurisdiction often leads to widespread confusion regarding the agency responsible for specific areas of law.[17]

3. CRISPR regulatory shortcomings

Ethical gray areas

Currently, the US Recombinant DNA Advisory Committee (RAC) will not consider germline alterations proposals, and scientists themselves issued a temporary self-imposed ban on CRISPR for human germline engineering until the safety risks of the procedure have been mitigated[19]. However, this boundary is not specified yet so there is tension between regulation for CRISPR application to embryos[19]. On the one hand, federal funding for CRISPR use on embryos is prohibited, but on the other hand privately funded embryo gene editing experiments are allowed that allows universities, small science organizations, and even bigger organizations that have enough funds to make embryo editing possible[20]. This happens because the guiding federal frameworks on CRISPR applications on human embryos do not exist[12,19]. While privately funded work has involved ethics committees and approval without overarching regulation of embryo genome editing there is a space in the privately funded world to transgress moral, ethical and legal spaces in embryo genome editing[9]. In other words, CRISPR research involving human embryos is stifled because of a lack of funding yet researchers are free to bend ethical boundaries in the realm of gene editing using CRISPR if they can secure private funding[18]. These conflicting outcomes represent a worst-case scenario.

Incorporating ethics into CRISPR regulation

Researching embryos is not a fully understood field, which naturally leads that gene editing technology, particularly for embryos, would not have any framework. First, the deficit model privileges expert definitions of the problem and of what is at stake over those of lay publics who nevertheless have to live with the consequences. The separation of 'ethical' and 'technical' aspects precludes meaningful discussion of the social contexts in which technologies are developed and made available[4]. Consequently, if we do not consider ethics alongside CRISPR development, we run the risk of prioritizing new technologies, corporations, and profit over the people and communities that may be affected by CRISPR, in ways that lack democratic legitimacy and may inhibit socially responsible innovation. Further, debates on effective governance solutions tend to remain the preserve of technical experts who may not have sufficient information to see the bigger picture. For example, if it becomes a moral obligation to edit all of our embryos to make the "best possible babies" as Savulescu and others have suggested, that would also require all women who want children to undergo IVF, a context which is not mentioned[4]. An open forum would be one certain example of a medium to support helpful debates for using CRISPR[19]. Setting the standard for who can participate would be the very first step of this discussion. There should be both people who affect and who are affected, which would include scientists, economists, doctors, governors, and patients who need this clinical trial. Considering the status quo that the government is not trying to intervene much about regulation, this debate should discuss the recommendations from small and private organizations that are not being materialized and not being legal policies[21]. In order to not fall behind the fast developing technology, the active inclusion of experts are required, and we should understand and analyze every detail about the process and aftermath of CRISPR[19]. Through debates, people would be able to include and structure policies that are just flowing around the society. This debate would help to extend and share ideas about CRISPR that is not only used for embryos but also for plants, animals, and food.

Cohesive overarching regulation

There are no strict or complete policies from the federal government that regulates CRISPR technology. Due to this ambiguity, there are different regulations at national and international level. Moreover, inside the US, the standard of regulation is not uniform. First, only the private funding allows for germline editing research instead of the broad public funding. Second, a gray area exists between expert recommendations and what the government enforces, and this can be seen in various regulations set by various private organizations without being influential. Consequently, this gray area leaves swaths of the industry unregulated[9,22]. For example, WHO emphasized the need for robust regulation in CRISPR and established a broad expert advisory committee on Developing Global Standards for Governance and Oversight of Human Genome Editing[9]. Supported by the governance framework on human genome editing, it allowed the set of recommendations in the area of leadership by the WHO and its Director-General, international collaboration for effective governance and oversight, human genome editing registries, international research and medical travel, illegal, unregistered, unethical or unsafe research and other activities, intellectual property, education, engagement and empowerment, ethical values and principles for use by WHO, and institutional, national, regional and global governance mechanisms for human genome editing[22,23]. Likewise, one authority should take the central

power and organize the regulations.

4. Who should have the authority over CRISPR?

Who should have the authority to make regulations?

To improve technology, medical scientists should play a big role. However, lawyers should question the mechanism of control over these processes as this is closely connected to human rights, ambiguous boundaries in embryo rights, and the responsibility issue about CRISPR technology. Therefore, the government should consider this technology more seriously. They should not only fund CRISPR development but also expect the availability, grants, economic benefits and harms, and potentials. In order to accomplish this, the framework of CRISPR should not give authority to one certain group of people but be discussed by various areas of people. Supported by the proactive government, regulatory agencies should regularly set policies and constantly review and keep up the fast paced technology. While adapting to new changes and development would be challenging, it should include the voices of scientists and experts as well because they know the most about the technology. The regulation should not primarily accept all ideas from people of medical areas as they can be inclined to the desire for developing new technology instead of the safer and widely accepted technology. Hence, new regulations of CRISPR should include voices of key actors such as doctors, patients, lawyers, etc, yet the government should be the primary and main part to make the regulation very influential and responsible compared to small voices and confusing policies from science organizations. Since the technology brings huge social impact, we should constantly consider the best way to guarantee safe and certain CRISPR technology.

Discussion

This literature review provided an analysis of 21 papers on potential harms, legal liminality and future regulatory direction of CRISPR technology, with a particular focus on CRISPR's impact on humans. The articles highlighted that not only do ethical concerns plague CRISPR technology and development, but no foolproof standards or wide-reaching policies currently govern CRISPR in the U.S. Without progressive, up-to-date policies, the literature review thoroughly shows that CRISPR development will quickly outpace legal regulations, an outcome that may have damaging ethical impacts. Many agencies dip their toes into regulation, recommendation and approval but by and large the federal and state governments are not playing a big role in ensuring the ethical and safety standards of CRISPR technology and its application. Scientists using human embryos as part of a CRISPR-driven research plan are incapable of receiving federal funding for the project, which leads them to either abandon research involving human embryos or seek private funding. Accordingly, researchers using CRISPR are often in the dark until they are readying products for market approval as to which laws will govern the product in which they have invested millions of dollars. To improve CRISPR regulatory frameworks, scientists should harness the knowledge of experts in diverse fields that intersect with CRISPR and create a strong governing body/agency to overlook genome editing policies. The other conflict is the commercial advantage and priority of fast development. Hereby, there is a need for public debate. Conflicts of interest usually are not disclosed in the context of public advocacy for specific research policies. This makes it very hard for participants in public discussions of ethical implications of the CRISPR technology to understand the actual economic interests in the background of certain advocated positions within the spectrum of risk-affirmative and risk-aversive positions. Since this issue can go to more political problems of legitimate representation, making a framework is a difficult task. There is currently no governing body at the federal level that is enforcing clear boundaries and restrictions around the use and development of CRISPR in different sectors. Decentralized, fragmented, and state-level regulation creates space for the misuse and abuse of genome editing as it makes it increasingly difficult to monitor CRISPR uses and enforce policies. To strengthen CRISPR policies, federal regulations will need to be informed by collaborations and discussions between all those who are impacted by CRISPR, including doctors, scientists, pharmaceutical companies, governmental institutions, and patients. To improve the presently fragmented regulatory system, a strong trustworthy federal governing body is necessary to create accountability and enforce robust, stringent, and unvarying regulations nationally. Secondly, while strict regulatory boundaries are a necessity, there should be flexibility for CRISPR policies to progress with the technology. Despite the fast-paced development of CRISPR, there is no space in the legal frameworks for policies to change in parallel to technological development. Since CRISPR is changing enormously year to year, it may not be reasonable for policymakers to keep up with every biomedical development in the field. There are some ways policymakers could continue to include CRISPR development as part of a set of progressive policies including frequent reviews of recent changes, involvement of field experts at every level of policy making, and flexibility in the writing of regulations that will accommodate new developments. Even though the main authority of the policy makers should overwhelmingly focus on humans, all the ethical issues should exist in various areas, and experts should apply these and make strict but flexible regulations. Lastly, the regulations should not only consider the present research but also about future findings by building successful regulatory frameworks for emerging technologies. Regulatory frameworks for

emerging technologies are difficult to build as the technology itself changes quickly. Regulation must keep up with the fast-paced progress to both avoid stymying cutting-edge research and to ensure future research benefits human well-being without transgressing moral or ethical boundaries. Besides the fast revolutions happening about CRISPR, it still has issues to solve in biological and bioethical terms. Off-target, after-effects, and human rights should be discussed and abuse of gene editing should be restricted through the dominant authority supported by experts in order to realize the further effect of CRISPR.

Methods

A comprehensive literature search was conducted using Google Scholar and PubMed to identify English-based articles published between 2019 and 2022 that met the inclusion criteria. The search was limited to articles within the United States to focus the review on a specific political and legal framework. The selection criteria required articles to be in English and within a four-year publication time frame, considering the rapid development of CRISPR technology. The search string used included keywords such as "CRISPR," "bioethics," "ethics," "morality," "gene editing," "USA," "policy," and "law," among others. A total of 21 articles were identified to fit the review based on the strict selection criteria. These articles were then downloaded and cataloged in Excel sheets for further analysis. All 21 articles selected for this review were literature reviews, chosen due to the extensive amount of scholarship available on the topic. Among these, two articles focused on providing a historical background, explaining the scientific process and highlighting the advantages of CRISPR technology. The remaining nineteen articles primarily discussed the bioethical and biological issues associated with CRISPR, including human rights considerations, off-target effects, future challenges, and the current legal framework.[10]

Conclusion

CRISPR is considered as groundbreaking medical technology that has the potential to save more lives. However, the US should set up strict boundaries and regulations in order to prevent any discrimination or issues regarding the impact of the technology. Pointing out the most serious problems that are already discussed or not yet discussed widely in the US, this paper encourages the development of CRISPR in a safer way both bio-ethically and medically.

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