The Proper Regulation and Use of CRISPR/Cas9 in the 21st Century

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Scientists battle to discover and create new, more efficient, and cost-effective technologies. The use of gene editing has been around since the 1970s but was very inefficient, expensive, and difficult to use (Doudna, 2015). A recent discovery could change the future of gene editing; Emmanuelle Charpentier and Jennifer Doudna, credited with the "discovery" of CRISPR/Cas9 technology, found CRISPR by studying a variety of bacteria and archaea (Doudna, 2015). From this discovery, a new genetic editing tool, CRISPR/Cas9, emerged. CRISPR/Cas9 allows for more economical, efficient, effective, and safe gene editing techniques. Vidyasagar (2017) says that CRISPR/Cas9 is "four times more efficient" than previous methods. CRISPR/Cas9 revolutionizes gene editing; however, not only does CRISPR/Cas9 affect our scientific future, but it also must be regulated and used correctly for the significant benefits to shine.

Currently, the world engages in a discussion of how to proceed with CRISPR/Cas9. Many different approaches require consideration. The scientific community must decide whether the benefits outweigh the costs and must determine whether to continue with a precautionary principle approach or a harm reduction approach with continued research and a focus on proper regulations. CRISPR/Cas9 technology revolutionized the medical field by opening the door to more efficient, accurate, and affordable genetic and genome engineering. Significant ethical implications arise that need consideration. In addition to the issue of unobtainable consent, there are many risks such as off-target mutations (unintended changes), societal divide, and inappropriate use. While all of these significant ethical and moral implications need

consideration, this paper will discuss the different approaches to CRISPR/Cas9 and how it must be regulated and used for maximum benefits.

Basic Information

Before any decisions get made about the future of CRISPR/Cas9, the public must first understand the basics. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. Cas9, a gene associated with CRISPR, works as "a specific endonuclease that cleaves off DNA" with RNA (Novella, 2016). In CRISPR/Cas9, the Cas9 enzyme snips through the DNA, and a small RNA molecule directs the "scissors" to the specific gene mutation to cut it (Ledford, 2016). In simpler terms, Cas9 recognizes DNA, cuts it out, and destroys the unwanted DNA with incredible precision, essentially allowing bacteria to detect viral DNA and eliminates the specific viral DNA before the virus can take over the bacteria (Doudna, 2015).

The specifics of how CRISPR/Cas9 works may seem complicated but remains a reasonably straightforward process. Many microbes use CRISPR to defend themselves against viruses. When a virus invades a bacterium, the microbe's cell gets a small amount of the virus's genetic material, cuts the DNA open, and places a piece of the virus's DNA into a spacer (a short portion of DNA that come from and match corresponding viral DNA parts). The CRISPR region (where nucleotide repeats and spacers are present) fills with virus DNA creating a "memory card" holding all the viruses previously in contact with the microbe. The microbe uses the virus's DNA to copy the genetic material each spacer contains and places it into an RNA molecule. Cas enzymes take an RNA molecule and "cradle it." Both the viral DNA and Cas enzymes move through the cell. When they detect the virus's genetic material matching the CRISPR RNA, the RNA attaches. Then, the Cas enzyme chops the DNA preventing any virus replication. This same concept can program enzymes to look for a specific short sequence of DNA and remove it

(Zimmer, 2015). The CRISPR/Cas9 technology works like a word processor: it finds the errors, removes them, and ultimately fixes the problem. (Kahn, 2016).

Various Ethical Problems

Many different ethical problems arise with the CRISPR/Cas9 system. Cosmetic applications cause the most ethical concerns. With a medical application, the intent seems more widely accepted. Novella (2016) says that the "emotional sense of what is 'natural' and 'pure'" provokes a bad reaction. As a society, we think of ourselves as humans in a very natural and pure state. If we disrupt this naturalness, people become concerned and disgusted. The concept of designer babies provokes these same emotions. Pang and Ho (2016) state that designer babies get created from "embryos selected by preimplantation genetic diagnosis (PGD)" or a baby genetically modified to change and influence the traits. These traits could, in the future, include gender, personality, physical traits, and intelligence. Lefferts (2016) reveals the concern of a "eugenics-focused society" with the introduction of designer babies and points out that the creation of "designer babies" could become a reality. Our society currently judges others based on looks and intelligence. If designer babies become standard practice, society will become inherently worse. Children today already have to meet many high and seemingly impossible standards; with designer babies in the mix, those standards will continue to skyrocket. The cosmetic application could lead to more significant societal gaps and a eugenics-focused society thus creating more social conflicts.

The idea of a societal divide between those who can both afford and decide to use CRISPR/Cas9 technology remains a genuine concern. An already staggering wage gap currently separates people in the United States and on a global scale. While CRISPR/Cas9 technology is cheap, 30 US dollars per gene sequence as stated by Tatay (2017), the more mutations in the

genome, the more sequences would require alteration. For some, even 30 US dollars would become a financial burden. The upper class and the high end of the middle class would not blink an eye at the cost; however, those 30 dollars could create serious financial troubles for the lower class and the bottom of the middle class. The concern of an even more significant societal divide remains valid due to this. While CRISPR/Cas9 provides a cheaper gene editing, for some, it may still be out of reach. Those who could afford it would continue to, while those who could not use it would be left behind, widening the gap.

Another ethical consideration remains in the altering of generations. With germline editing, changes get passed down to future generations. This application could help reduce any anxiety for prospective parents that carry a genetic mutation that could cause disease in their children. With CRISPR/Cas9, heritable diseases could essentially get eliminated. However, ethical problems arise with informed consent laws in inheritable change. Informed consent is a critical aspect of any medical treatment. Morris (2017) states informed consent as the responsibility of medical professionals to notify the individual of all the inconveniences and hazards in addition to the effects. If heritable changes occur, the future generations do not receive informed consent. However, until the age of 18 in the United States, parents make decisions and give the informed consent for their child. Rodriguez (2016) raises the question of whether parents should decide their children's essential genetic future. Although the benefits could change lives and prevent children from having to deal with terrible diseases, do we hold the right to dictate the future of generations?

Application

The current applications of CRISPR/Cas9 technology include plant breeding for agricultural purposes and breeding animals and microorganisms for bio-economy and

biosecurity. One application that Fears and Muelen (2017) discuss is the "simultaneous edits of multiple genes" in plants, which increase crop quality. A more recent application reduces browning in mushrooms, and many more GMO (genetically modified organisms) products continue to emerge with greater precision. Currently, CRISPR/Cas9 is used in animals, specifically mice and monkeys, for health improvement and basic or biomedical research as reported by Doudna (2015). Other possibilities such as enhancement of and an increase in agricultural production exist. Fears and Muelen (2017) discuss the "biosynthesis of pharmaceuticals, other high-value chemicals and biofuels, and biosensors" in microorganisms. These many different applications make it a versatile technology.

Many other possible applications in plants, animals, and microbes have become available with CRISPR/Cas9, especially in humans. In humans, CRISPR/Cas9 would find the mutation, cut the mutated sequence out, and the proper sequence would get inserted. If a mutation causes disease, CRISPR/Cas9 will eliminate the mutation, eradicating the disease and completely changing how diseases caused by mutations get treated. Tatay (2017) states that scientists created an ongoing list of creatures in which the use of CRISPR/Cas9 took place, currently consisting of 36. This list will continue to grow in conjunction with the increased application of CRISPR/Cas9. If a human application of CRISPR/Cas9 occurs, not only would the number skyrocket, but the possibilities would become endless, making it a critical decision.

Potential Applications

Many different CRISPR/Cas9 applications continue to arise and expand the possibilities towards human applications. The two human applications include somatic and germline editing. In somatic cells, the changes do not get passed on to future generations and occur after birth. Somatic editing remains less controversial than germline editing due to the lack of generational

change. Somatic editing allows the individual to both see the results and decide for themselves whether or not they want the changes. In germline editing, the changes occur in the embryo and get passed on to the future generation (Botella, Hurlbut, and Newson, 2017). Germline editing affects many generations, which creates problems with informed consent by allowing the creation of a person with modifications that they might not want. The ethical issues for germline and somatic editing differ based on the different application techniques and results, creating questions surrounding the regulation of specific applications of CRISPR/Cas9.

Regarding consent, parents make important decisions for their children's health: they decide whether children will get vaccinations, which treatments such as antibiotics and other medications they should receive, and whether operations will occur. The child has no say in what they want. Thus, the application of CRISPR/Cas9 is no different. Rodriguez (2016) discusses that CRISPR/Cas9 application in zygotes or early-stage embryos allowed application of changes in all the cells in the body and passed on to future generations effectively erasing the mutation from that generational line. Couples see genetic counselors to determine the risk for their children of genetic diseases and decide whether or not to reproduce based on those results. With CRISPR/Cas9, those children would get to live. Somatic editing would allow for a change in genes; however, it would only be permanent in that individual. Parents can give consent for their children on all other medical decisions, and technology could increase the improvement of their child's life.

In addition to somatic versus germline, applications can vary in whether CRISPR/Cas9 gets used for medical or cosmetic treatment. Kang, Caparas, Soh, and Fan (2017) discuss how the medical application could minimize the global strain stemming from currently incurable diseases. It would ultimately benefit millions of people. Doudna (2015) highlights the possibility

of producing stronger bones and lessening susceptibility to many diseases such as cardiovascular disease. Hiltzik (2017) also states that CRISPR/Cas9 could help reduce the rejection risk in transplantation of organs from animals to humans (xenotransplantation). Achenbach (2017) reports that CRISPR/Cas9 could be used to "prevent congenital diseases but could also get used for cosmetic enhancements." A cosmetic application brings more concerns than a medical application. Novella (2016) discusses the possibility of producing "stronger, smarter, taller children" and dictating eye and hair color. The cosmetic changes could lead to a eugenics-focused society, and the issues surrounding that discussed previously in this paper. These two different approaches bring their problems, but both need serious thought and consideration.

As CRISPR/Cas9 gains popularity, more and more studies and experiments get published. Studies and trials play a significant role in the application and regulation of any technology, especially CRISPR/Cas9. As stated by Baylis and McLeod (2017), these studies and trials get used in establishing credibility as well as internal, external and construct validity before things get brought to in-human clinical trials. A Chinese research team recently "attempted to edit the genes in human embryos" (Novella, 2016). Maron (2017) reviews an experiment done by the Oregon Health & Science University team that used CRISPR/Cas9 to correct a genetic mutation that leads to embryonic heart failure. They found that this "caused no apparent errors" in the genome (Maron, 2017). Kang, Caparas, Soh, and Fan (2017) also explains a recent paper published by Hong et al. that showed "genome editing was carried out in human preimplantation embryos, resulting in embryos without mosaicism and off-target mutations." The lack of mosaicism and off-target mutations suggests CRISPR/Cas9 holds the ability of effective and safe heritable germline correction without making unintended edits (off-target mutations). Also, Kang, Caparas, Soh, and Fan (2017) discussed current human clinical trials that use

CRISPR/Cas9 technology to combat lung, prostate, and renal cancers. Doudna (2016) discusses an experiment conducted in Philadelphia where scientists used CRISPR/Cas9 to remove integrated HIV from patients. Pothier (2017) shows a study in which the use of CRISPR/Cas9 resulted in treatment more effective than chemotherapy and with fewer side-effects for a mutation in the HER2 gene that shows up in 25 percent of breast cancer patients. While these experiments and studies remain controversial and in the infancy of future research, they remain imperative and must continue.

Arguments

Many different approaches to CRISPR/Cas9 require serious thought. Some people believe that we should completely stop all research on CRISPR/Cas9. Whether they think the ethical or moral issues seem too high or the risks outweigh the benefits, a serious discussion needs to occur. Some believe that we cannot just stand around waiting for regulations. They think we should move on, full steam ahead, and discover CRISPR/Cas9's real potential. In their eyes, the benefits greatly outweigh the risks and pausing could ultimately hinder our progress. As usual, a neutral group exists, believing that we need to err on the side of caution while moving forward and taking a real look at the costs and benefits to understand what dangers might lie ahead. Each of these views deserves consideration and brings various aspects to an ultimate decision that could bring about change in the course of medical history.

The Precautionary Principle Approach

Some argue that the precautionary principle must occur with CRISPR/Cas9 technology, altogether stopping not only due to ethical, moral, and religious reasons but for safety concerns. The ethical and moral debates surrounding genetic engineering arise again, and with anything unfamiliar, hesitation and doubt occur. By mixing this unfamiliarity with religious, ethical, and

moral beliefs, things can get much more complicated. Due to some viewing the use of embryos for research a violation of life, the scrutiny continues. In addition to this, the issue with informed consent makes things difficult. Typically, if a medical treatment or procedure occurs, the patient receives all the information about what happens, possible side-effects and risks. With germline editing, future generations become affected without choosing whether or not they want to take the chance. Because unknown risks might occur, people believe that a complete stop must happen to protect humanity.

Besides the ethical, moral, and religious aspects, people favor the use of the precautionary approach, which essentially states that if a technology holds possible, unknown risks, it should be banned. Some of these risks include off-target effects and mosaicism. According to Genome.gov (2017), the risks of off-target effects (when edits occur in the wrong spot) and mosaicism (when only some cells receive the edit) need careful consideration for safety, especially the possibility of off-target effects and mosaicism being passed down through generations. Kahn (2017) says that scientists could build a reversal drive that would cancel any mutations out; however, it is only a theory. Charpentier (2016) says that the "risks attached to the new possibilities" cannot be fully understood yet. These risks lend themselves to the idea of the application of the precautionary approach.

These arguments, however essential and real, do not appear very realistic. Novella (2016) argues that people's "worst fears never manifest." In studies and experiments, as shown by Wrigley and Newson (2018), donors of the embryos, eggs, and sperm received "full ethical approval," and the donors provided informed consent in these studies and experiments. An issue with using embryos for testing is that they do not grow into a child. People argue that this is a form of abortion which, as stated by Kolata (2014), brings a significant question regarding

parent's moral choices in discarding an embryo. Vasiliou and Diamandis (2016) reveal that some benefits of CRISPR/Cas9 technology include the reduced risk to embryos and a reduction in abortions, whether unintentional (miscarriage) or intentional. Due to the prevention of deaths and the increased quality of lives, we should seize this opportunity. The chance of the unknown risks occurring remains little to none. While the precautionary approach could prevent any potential dangers, we would deny the plethora of benefits that could completely change people's lives for the better.

A Full Speed Approach

Another argument for CRISPR/Cas9 technology involves continuing full speed ahead. Kang, Caparas, Soh, and Fan (2017) say CRISPR/Cas9 holds "great potential in next-generation therapeutics." CRISPR/Cas9 can change the course of medicine. The advancements and the current ability to change essentially any part of the human genome with great precision and accuracy makes it revolutionary. Wrigley and Newson (2018) point out that the use of CRISPR/Cas9 in humans "may soon become a reality." Caplan, Parent, Shen, and Plunkett (2015) showcased the many potential therapeutic applications ranging from infectious diseases, stem cell models, repair of fatal defects in embryos, and cancer immunotherapy. Some believe that with so many benefits that greatly outweigh the risks and many opportunities, we should forge on. CRISPR/Cas9 technology still has not been used to its full potential; if regulations and caution get applied, we may never discover its full potential.

Despite the tremendous potential benefits, serious risks need consideration. Off-target mutations could be harmful. Zhang, Tee, Wang, Huang, and Yang (2015) describe in simple terms that an off-target mutation occurs when an unintended gene receives an unintended mutation. These unintended changes could ultimately result in a different sequence, possibly

causing harm. Scientists are currently discussing a reversal system where these off-target mutations could get reversed, but at the moment, it is only hypothetical. Kang, Caparas, Soh, and Fan (2017) discuss the International Summit on Human Gene Editing held in Washington in December of 2015. At this summit, a large part of the discussion included the need to evaluate the concerns, possible impacts on society, and the need for benefits of CRISPR/Cas9 applications to outweigh any risks significantly. Hiltzik (2017) brought up the global accessibility of CRISPR/Cas9. In addition to the extensive availability, it does not require a sophisticated knowledge of equipment; Doudna (2015) even stated that an intelligent high-schooler with an advanced lab could use CRISPR/Cas9. This availability creates the risk of the technology getting into the wrong hands and the possibility of incorrect and harmful use. These risks need serious consideration and cannot merely get brushed aside.

Harm Reduction Approach

Another viewpoint is the harm reduction approach. Caution may seem like the cowardly way to approach things; however, these risks need consideration. Going full steam ahead would only exacerbate concerns and improper uses. Harm reduction creates practical strategies and plans to help reduce any negative consequences occurring from a technology. According to Kang, Caparas, Soh, and Fan (2017), a complete ban would hinder the development of future treatments and, due to the high accessibility, would be completely unrealistic. Neither continuing full speed ahead nor completely halting provide the best option. Maron (2017) explains that the National Academics of Sciences, Engineering, and Medicine recently released a statement that states the need for a broad public agreement concerning the safety of clinical work. For this to happen, Wrigley and Newson (2018) state that “regulators, funders, scientists, and editors” must work together to create a path for responsible use of CRISPR/Cas9. The importance of proper

regulation and communication may seem trivial but holds extreme importance. Due to this importance, harm reduction appears as one of the better options.

Media and Literature

Many authors and directors create books and movies based on the future containing genetic editing. The film Gattaca (1997) shows the potential society that could occur with the use of designer babies. The part of the population that received genetic editing before birth appeared 'better' and gained better jobs and status. Those that did not receive genetic editing appeared inferior and could only get positions deemed unimportant such as custodial work. In Brave New World (1932), Huxley also illustrates this concept of genetic engineering being the superior state. People who receive genetic engineering live normal lives, while people who did not receive genetic engineering live on reservations, leading inferior lives as outcasts. In Blade Runner (1968), Dick takes an opposite approach. Those who received genetic engineering, the androids, get viewed as slaves and property. If they do not obey, the non-genetically engineered humans kill them. Those who did not receive genetic engineering were superior. Despite the classifications of fiction and the two opposite outcomes that may or may not occur, the importance of these warnings is worth considering.

Regulations and the Correct Use

Regulation

According to Genome.gov (2017), 40 countries in 2014, including 15 in Western Europe, either discouraged or banned any research of germline editing. Pothier (2017) reviews the stages required for the establishment of regulations. These stages include a pre-clinical trial, a clinical trial, NDA review (FDA's new drug application review), and post-marketing (FDA's post-approval risk assessment). For these steps to even begin, four main things must get provided:

funding, support, training, and participants. Without these four things, regulations will not occur. Regulations take time and can push back any progress which causes some to want to skip these steps and continue forward. Another issue with the current regulation process, as stated by Vasiliou and Diamandis (2016), is that the scientific, corporate, and political elites participate in the policy and ethical deliberations, and the public does not get the proper education; however, appropriate regulations do not occur, severe risks and improper uses may take place. Even though regulations might slow down progress, they play an essential role.

For proper use of CRISPR/Cas9, useful regulations could make or break our future. According to genomeweb.com (2017), the US Senate Committee on Health, Education, Labor, and Pensions held a hearing to discuss regulations for CRISPR/Cas9 technology; the hearing concluded that creating regulations must occur in the United States to prevent incorrect regulations from being created by other countries. The problem with regulations remains the complexity of how and where they occur. Fears and Meulen (2017) bring the idea of sector-specific application regulations. This application would allow regulations for specific aspects and workings of CRISPR/Cas9 rather than regulating gene editing as a whole. For CRISPR/Cas9 to even become a possibility in human applications, specific regulations need to occur.

In addition to "how," the importance of "where" remains. If the United States does not set regulations, somewhere, someone will set the boundaries and regulations. Nicol et al. (2017) state that regulations should occur consistently and globally. The United States currently holds an enormous influence on many different countries, so if the United States establishes regulations, others will follow. If the United States does nothing, other countries will create their regulations, possibly putting humanity at risk if not regulated properly. Genomeweb.com (2017) discusses that if regulations get too strict, science will either go outside the borders or

underground. Science forced underground could cause severe issues regarding the safety and accuracy of results and tests. If science goes underground, any regulations currently in place could get ignored. Not only would regulations and laws become lax, but the tools needed to perform accurate tests would also prove more difficult to acquire. In addition to the safety and accuracy problems that could arise, scientists would communicate less with each other, thereby reducing the amount of collaboration. Both of these options put the population at risk. Proper regulations are critical to the safety and progress of CRISPR/Cas9 technology, and the United States must instate.

The United States needs to instate proper regulations. We cannot take chances with the safety of the population, which is why neither stopping nor full speed would not work. Nicol et al. (2017) state that "regulations must be sufficiently flexible and technologically adaptive to address new technological advances and applications as they arise." With the constant change of technology, regulations need flexibility and stability to stay relevant and effective. If regulations get too strict, scientists will not hold enough power to progress; however, if regulations do not occur, we place too much trust in the unknown. The risks of off-target mutations, cosmetic application, and consent issues need serious thought and consideration in addition to regulations specifically tailored to these possible risks. The benefits of CRISPR/Cas9 technology for medical purposes could change the future of medicine. We need to regulate CRISPR/Cas9 technology and require more experiments before a clinical application occurs. The United States needs to get regulations out promptly to prevent underground science and other countries creating improper regulations. Regulations on solely medical applications would allow safe advancements.

The Correct Use

Once different opinions and regulatory approaches have been discussed, it is important to look at the appropriate approach and reputational steps that must follow. With all three differing views and opinions, people must understand logical thoughts, concerns, and arguments exist within each argument. However, many of those concerns and arguments would most likely never occur. To make an informed decision, people must look at all aspects. After reviewing three main sides of different applications, one application holds the most significant potential: the harm reduction approach - a cautious, regulated approach.

CRISPR/Cas9 holds countless possibilities to change the future of medicine. These possibilities to prevent many life-changing diseases are too good to pass up. While many valid arguments as to why CRISPR/Cas9 should halt hold importance, the benefits significantly outweigh the "what if" statements. Regulations would help prevent inappropriate or unsafe uses. For now, cosmetic use should not occur until full ethical reviews get completed. For the best use, medical applications to fix genetic mutations that cause disease needs to occur; to not use CRISPR/Cas9 to help eradicate genetic diseases is a mistake.

To ensure the medical use of CRISPR/Cas9, specific regulations need implementation. Since regulating genetic editing as a whole effectively and properly could not happen, CRISPR/Cas9 must get regulated as a specific technology. To use CRISPR/Cas9, medical facilities must be required to obtain a license allowing only medical applications (fixing existing genetic mutations causing disease). In addition to the license, a global panel consisting of scientists and doctors should meet to determine an exact list of the genetic mutations that cause diseases, and which do not. This would help put in place global cooperation which is imperative. Without specific regulations and global cooperation, CRISPR/Cas9 would not reach its full potential.

Ultimately, CRISPR/Cas9 technology will change our future. We can eradicate many genetic diseases, cancers, and more. The use of CRISPR/Cas9 for cosmetic reasons raises concerns. In addition to cosmetic applications, the possibility of off-target applications and improper use could be detrimental to society. For proper regulations globally, the United States needs to set the standards. Regulations need to be strict enough to prevent unwanted uses but not too tight as to drive science out of the boundaries or underground. The importance of proper regulation, use, and discussions all play crucial roles in the future of medicine.

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