

# The Usages, Risks, and Ethics of CRISPR/Cas9 Technology

Amber Rudenick

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CRISPRs (clustered, regularly interspaced, short palindromic repeats) are short DNA sequences with unique spacer sequences that, along with CRISPR-associated (Cas9) proteins, make up an adaptive immune system in many bacteria and archaea against invading bacteriophages (Rath, 2015). Resulting CRISPR technology holds great promise in fields such as animal disease modeling, material science, genetically modified plant technology, biofuel technology, gene therapy, and drug development. A standard molecular biology laboratory can now edit genes or whole genomes of many organisms, as CRISPR/Cas9 does not require sophisticated knowledge or expensive equipment.

Yet, CRISPR raises many ethical issues, not all of which concern only humans, but also other species and the environment. Off-target mutations are currently observed at great frequencies, which may cause genomic instability and disrupt the functionality of otherwise normal genes. Socially, there will also be a problem if some populations or individuals are enhanced, genetically having advantages over others. Once genome editing reaches a high enough safety level to allow clinical applications, further discussion will be needed, considering the social, legal, and ethical implications, and the need for regulatory norms to avoid abuse of genome editing in any form.

## **Background**

By using short RNA molecules as a template, Cas9 makes highly sequence-specific cuts in DNA molecules that can be exploited to insert genes or to precisely modify the nucleotide sequence at the cut site. CRISPRs were first identified in the 1980s (Ishino, 1987), but it is

only during the past few years that scientists realized their potential to edit the genomes of any organism, even human embryos. The CRISPR/Cas9 system recognizes its target sequence via guide RNA molecules that can be cheaply and easily synthesized.

### **Function and Origin of the Crispr/Cas9 System**

The CRISPR/Cas9 system is a prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and bacterial viruses. CRISPR consists of short repetitions of DNA sequences followed by short segments of spacer DNA, originating as a result of a bacterial virus or plasmid. The cas (CRISPR-associated) genes code for nuclease or helicase proteins associated to CRISPR repeats with the function to cut or unwind DNA (Jansen, 2002). The CRISPR system also stores DNA sequences from invaded viruses or plasmid, and when the same type of virus invades again, the system recognizes it using the transcribed RNA sequences and directs a cas nuclease to cut the DNA.

Cas9 was isolated from bacterium *Streptococcus*, and is able to cut DNA in two sites at each strand of the double helix of the DNA. Doudna and Charpentier discovered that bacteria respond to invading phages by transcribing spacers and palindromic DNA into a long RNA molecule which is cut into pieces (called crRNAs) by using trans-activating RNA (tracrRNA) and protein Cas9 (Doudna, 2014). Later it was discovered that the combination of tracrRNA and spacer RNA into a single guide RNA mixed with Cas9 could be programmed to find and cut specific target DNA segments, thus provided with the ability of gene editing (Jinek, 2012).

### **Balance of risks and benefits**

An important ethical issue in research is the benefits must be greater than the risks. Greater attention must be place on risks, since they may damage living beings or the environment. The application of CRISPR/Cas9 technique involves the risk of producing off

target mutations, which can cause deletions. Large genomes may contain multiple DNA sequences identical or very similar to intended target DNA sequences. CRISPR/Cas9 may also cleave these unintended sequences, causing mutations which may lead to cell death or transformation. Further efforts need to be made to reduce off target mutations, especially for precise modifications needed for therapeutic application. Another important problem is the efficient safe delivery of CRISPR-Cas9 into cell types or tissues that are hard to transfect and/or infect.

### **Ecological disequilibrium**

In experiments using RNA-guided gene drives based on CRISPR/Cas9 technique, it is necessary to probe specificity considering off target effects as a possibility. Since gene drive is still operating in created beings, the possibility of mutations being off target continues and may increase each generation. If there is risk of transferring genes to other species, then there is risk of transferring modified sequences, passing the negative trait to related organisms.

The dispersion of gene drive traits may be difficult to control. The disappearance of whole populations targeted by gene drive can carry drastic consequences in the ecosystem equilibrium. For example, other plagues may be developed. This demands the careful assessment of each potential application and the need of regulatory norms. Safety measures are necessary in order to avoid the extinction of organisms that may cause ecological damage or affect human health.

### **Application of CRISPR/Cas9 technique to human germline**

Ethical concerns have been raised regarding the possibility of genome editing in human germline cells (this is the genome that can be transmitted to following generations). Until now, all therapeutic interventions in humans using genome editing has been performed in somatic

cells, but the experiment of Chinese researchers Liang and collaborators has created concern over the possibility of making changes in human germline (Liang, 2015). This difference lies in that intended therapeutic genetic modifications in the germline may be transmitted to following generations.

In general, therapeutic genome editing interventions in somatic cells are ethically accepted, but germline cells are not the same. Since the CRISPR/Cas9 technique can produce mutations and side effects, unpredictable changes may be transmitted to future generations. Also, there are problems in how to implement informed consent when there are risks and the effects could be transmitted to several generations. Hence, many scientists support basic research on CRISPR in cell lines or in somatic cells, but do not see CRISPR as developed enough for any clinical use in making inheritable changes to humans (Lanphier, 2015).

In December 2015, the International Summit on Human Gene Editing, which gathers members of national scientific academies of America, Britain and China, discussed the ethics of germline modification. They agreed to proceed further with basic and clinical research under appropriate legal and ethical guidelines, but altering of gametocytes and embryos to generate inheritable changes in humans was claimed irresponsible (Steven, 2015). However, in February 2016, British scientists were given permission by regulators to genetically modify human embryos by using CRISPR/Cas9 and related techniques only for research (Gallagher, 2016).

Currently, the risks of heritable unpredictable genetic mutations are greater than the possible benefits of therapy. The technique should be fully safe in order to try therapy in the germline. Furthermore, if damage were introduced, there will be a problem to whom make liable for the damage done to following generations. Once genome editing reaches enough safety level to allow clinical applications for preventing the development of genetic diseases,

further discussion will be needed, considering social, legal, and ethical implications. and the need of regulatory norms to avoid abuses of germline genome editing.

### **Genome editing for enhancement**

CRISPR/Cas9 offers new possibilities to render humans immune to a range of diseases, or to repair fatal gene defects in a human embryo. Another ethical issue put into play, as a result, is the possibility of non-therapeutic genome editing. The efficiency of the CRISPR/Cas9 technique increases the interest to change genetics in accordance with our life interests. This could be used to enhance the performance of athletes, to prevent violent behavior, or diminish addiction. If the intervention is done during development, there can be problems of consent with minors. It will be questionable if parents or guardians should be allowed to decide for them their future for non-health reasons.

The mandate to mold our children, to cultivate and improve them, complicates the case against enhancement. We usually admire parents who seek the best for their children, who spare no effort to help them achieve happiness and success. If it is permissible and even admirable for parents to help their children in this way, why isn't it equally admirable for parents to use whatever genetic technologies may emerge to enhance their children's intelligence, musical ability, or athletic prowess?

Another thing that interested me was how technology such as this will affect equity. As gene editing becomes a societal norm, those who do not have enough money to purchase it will be put at an innate disadvantage. Socially, there will be a problem if some populations or individuals may be enhanced genetically having advantage over others, for example, in intellect. Our educational systems will change drastically if everyone has a computer within their head. Therefore those who do not have access or means to get such technology will not

have access to education, which will create an even greater wage gap and increasing poverty level.

Some who worry about the ethics of cognitive enhancement point to the danger of creating two classes of human beings: those with access to enhancement technologies, and those who must make do with their natural capacities. If the enhancements could be passed down through generations, the two classes might eventually become subspecies- the enhanced and the merely natural. Worries about access ignore the moral status of enhancement itself. Is the scenario troubling because the unenhanced poor would be denied the benefits of bioengineering, or because the enhanced affluent would somehow be dehumanized? The fundamental question is not how to ensure equal access to enhancement, but whether we should aspire to it in the first place.

### **Changing of Normalization**

Tremendous pressure has been exerted to expand the concept of disease in order to make enhancement techniques more acceptable to the general public. This new definition would bring in the perceived psychosocial effects of others without the enhancements being considered “less than perfect”. Where is the line between aiding the sick and suffering, and changing the human condition? For example, there has been a rapid expansion of diagnoses of ADHD. In 1990, 900,000 children were using Ritalin. By 1997, it was 2 million. By 2000, 3.5 million were using Ritalin, with another 1.4 million using other related stimulant drugs (Diller, 1998). Why such a rapid rise? Some suggest that ADHD is not really a disease at all, but a diagnosis for a collection of normal childhood behaviors (Diller, 1998).

Drugs such as this, within the enhancement debate, are not a source of recreation but a bid for compliance- a way of answering a competitive society's demand to improve our

performance and perfect our nature. This demand for performance and perfection raises the bar for “normal” behavior or traits, changing all of society’s perspectives as a result.

### **Formation of animal chimeras for organ transplantation**

The development of human/animal chimeras for organ transplantation may provide hope for many that have to wait for a human organ donor. However, the formation of these chimeras may carry human neural and germ cells (Polcz, 2016). Chimeras have raised ethical concerns over their risk and on the violation of the order of nature, producing moral confusion on how to treat the organism, as animal or as human? For some, chimeric embryos possess the potential to develop organisms with human-derived cells or tissue, which may affect the identity of the human species, and our perception of its dignity. If an organism contains human cells, it does not necessarily convert the organism into human, and should not affect its dignity. The human like characteristics associated to the chimera are only of biological nature, and it should not affect the moral status of the animal.

### **Ethics of Cloning**

There was a story that was released recently by NPR (Stein, 2018), that discussed how researchers in China had cloned primates for the first time. They had cloned two monkeys by taking the DNA from the nuclei of fetal monkey cells and putting the genes into monkey eggs that had their own DNA removed. The scientists then stimulated the eggs to develop into embryos, which were placed into the wombs of female surrogate monkeys to develop into baby monkeys. It's the first time the technology (somatic cell nuclear transfer) had been used to clone any close relative of humans.

This development could prove to be quite useful. Genetically identical monkeys can be used to study many human diseases, especially brain diseases such as Alzheimer's or

Parkinson's. Yet, this progress also raises the concern that someone might try to use the same technique to clone humans, given the biological similarities between monkeys and humans. Many think it would be highly unethical to even try to clone a person the same way. For example, most of the cloned Chinese monkeys died in the womb or soon after birth. The safety of the resulting child is the number one concern.

There are many potential risks, as cloning creates identical genes. This prevents gene diversity. Reducing the diversity of genes weakens the ability to adapt. While human cloning allows genetic mixing with humans, it also makes the reproduction characteristics likely to be undesirable. The clone and cloned individual will have similar genes, traits, and personalities even though they may be raised differently.

Clones may also be treated as second class citizens, which are only created as organ donors. If people are cloned, the clones will hopefully receive the same rights as any other human being. Sophia, a humanoid robot, already has citizenship in Saudi Arabia. This suggests that Sofia, a citizen, is a "person" and is therefore also entitled to all the rights of other citizens. I wonder how the rankings of clones will compare to robots within the next few years, and the extent of rights that they will be able to achieve.

The Roman Catholic Church condemns the practice of human cloning. They believe it represents a grave offense against human dignity and equality among the people. Fukuyama (2002) thinks that reproductive cloning should be banned outright, and that we should draw the line before this happens, as it will create moral and societal problems. There is an aversion to human cloning, with many people thinking that a clone would not be a real person, that cloning is "playing god", or that cloning is not natural. Therefore, current research on the subject is extremely limited. Yet, cloning is the opening wedge for a series of new technologies that will

ultimately lead to designer babies. Therefore I think that people may eventually open up to it to an extent.

Cloning raises the prospect that reproductive decisions will suit the interests of the parent rather than the child. Does this mean that we are taking those rights away from the child, and that the government should intervene? Yet, we can say this same thing about anything that a parent chooses of their child at a young age, such as getting their ears pierced. The decisions of a parent are assumed to be made in the best interest of the child and, therefore, aren't withheld. These ethical issues of human cloning will become an important issue in upcoming years.

### **Applications of animals in CRISPR**

Some applications of CRISPR in animals improve current standard practices in the biomedical sciences. For example, some research projects require animal lines that are specifically bred for certain mutations. Using CRISPR to generate these lines produces less genetic variability than standard breeding techniques and helps researchers to introduce mutations that more accurately represent the human genetic defects they study (Larson, 2014). Though there are standing ethical issues implicated by this practice, such as animal welfare, using CRISPR for this purpose does not challenge existing regulations of laboratory animals.

Other applications in animals, however, pose ethical concerns. In particular, CRISPR could be used to replace methods of genetic modification to improve food for human consumption. Research groups and private biotech companies are currently assessing whether such genome edits are feasible and safe. It is not clear exactly what criteria the FDA- or any other agency involved- uses for assessing the safety of genetically edited animals for human consumption. These regulatory processes must be more transparent and accountable.

## **Gene drive and CRISPR**

There is another, potentially much more dangerous and controversial, application of CRISPR: the possibility to potentially eradicate disease by exterminating disease vectors and invasive species. Researchers are exploring gene drives to block disease transmission to render species incapable of carrying diseases. Others aim to induce sterility to prevent reproduction, or limit the lifespan of their offspring. Such methods could effectively destroy an entire species and could have significant environmental consequences.

Gene drive is a powerful tool that makes it more likely that the edited trait will be passed on to offspring through sexual reproduction. The introduction of a few edited animals is unlikely to have much of an effect. However, gene drive actively copies a mutation made by CRISPR and thereby ensures that all offspring and subsequent generations will inherit the edited genome. Over generations, this would lead to an extremely noticeable effect. The use of gene drives, though, also poses a much larger risk to the environment, as they have the potential to decimate an entire species, eliminate a food source for other species, or promote the elimination of invasive pests.

## **Genetic Enhancement in Media**

There are many instances of genetic enhancement within media, specifically in the science-fiction genre. This leads to many different portrayals of it, and can influence the public's view of such as a result. Within *Robopocalypse* (Wilson, 2011), robots gained control of society by killing off the humans "for the greater good". As a result, those who had robot parts put onto them, the "transhumans," were discriminated against by other humans. Even if the enhancements were for improvement, they were still considered foreign, making them considered less human as a result.

The novel *Brave New World* (Huxley, 1932) showed that in order for a utopian society to achieve a state of stability, a loss of individuality, and the undoing of our current morals and ethics must occur. Children are born and genetically modified in state facilities where, according to what social class they will be, are given or denied certain elements that are critical to proper development.

The importance of the individual is near zero in this world. In the end, the society has erased the individual and at the same time ceased human growth, even though they themselves think they are expanding humanity. Loss of identity is a large result of genetic engineering within this novel. This ensures that early on in life there are few, if any emotional ties. Everyone in the Brave New World is essentially parentless. This leads to their society being controlled exactly the way that the government wants, and with less variation (with genetic engineering) than if they had used drug enhancement to progress.

### **Genetic Enhancement and Religion**

Religion supplies rules that we tend to accept as basic human values. These rules have extreme impact, having shaped politics, sciences, and almost all of history. Religion plays a large role in society's definition of what it means to be a human being. This has an extensive impact on society's view of genetic enhancement, as many religions caution against it.

According to Jesus Christ's teachings, we were made in god's image, and thus this is a source of human dignity. Genetic enhancement can be viewed as changing god's perfect creatures, created in his image. Enhancement therapy involves not the healing of disease, but the improvement of average or less than average characteristics. Hence, no longer is it a case of fixing a broken part, but of adding something new to a normally functioning system. This then does not fall under the Christian category of "healing the sick" (Matthew 10:8).

Jesus Christ also says that humans are both finite and sinful. We lack both the wisdom and purity necessary to decide matters of human “perfection.” It is, therefore, immoral to use such genetic technologies as human eugenics and human cloning. Thus, from the perspective of Christians, a theology of health and disease (as opposed to enhancement) must be developed in accordance with sound biblical guidelines.

In Buddhism, it is said that you must combine compassion with wisdom. One without the other is incomplete. This would seem to be especially true when it comes to genetic engineering. From the Buddhist perspective, we are all connected through a vast web of interconnectedness. For Buddhists, this is true not only from a spiritual perspective, but it is also true from an environmental perspective.

Subsequently, you can't change one thing without affecting everything else. One of the unknown dangers of introducing genetically altered plants and animals into the environment are the potential dangers of long-term human consumption of those modified foods. So asking if genetic engineering is morally right or wrong is the wrong question to ask. Instead we should ask if genetic engineering is being conducted in a careful and responsible way so as not to harm the environment or us.

### **Conclusion**

CRISPR technology holds great promise in fields such as animal disease modeling, material science, genetically modified plant technology, biofuel technology, gene therapy, and drug development, yet raises many social, ethical, and safety issues. These issues do not concern only humans, but also other species and the environment. Additionally, the distinction between therapy and enhancement, the debate of cloning, religious views, gene drive's effects, applications of animals, human equity, societal consequences, and ecological equilibrium are

all important aspects that need to be examined in detail before extreme application of genome editing.

Once genome editing reaches enough safety level to allow clinical applications, even further discussion will be needed, considering social, legal, and ethical implications and the need of regulatory norms to avoid abuses of germline genome editing. It will be difficult if not impossible to muster support for any effective restrictions until we begin to experience the societal problems that genetic enhancement will create, so it is important to consider what restrictions would be appropriate now, how they would be imposed, and what changes would be needed in existing laws and institutions to facilitate them.

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