Germline Gene Editing: The Pandora's Box of the 21st Century

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Introduction

As a global scientific community, we are rapidly approaching an ethical threshold that will become one of the toughest moral dilemmas of the 21st century. This Pandora's box, better known as editing the human germline via CRISPR-Cas9, is quite literally, a life-altering technological innovation in the field of genetics. When CRISPR (short for clustered, regularly interspaced, short palindromic repeats) is paired with a Cas9 protein and an RNA template, it can cut, paste, and read any gene location on a strand of DNA (Benston, 2017). It is efficient at targeting several DNA sequences at the same time, with its accuracy and low cost earning it the title of revolutionary tool by the scientific community. It will enable scientists to better understand the genomes of plant and microbial life, as well as the genetic makeup of animals (Olson, 2015). CRISPR will also play a growing role in the medical field in generating animal models of multifactorial inheritance disorders such as heart disease, diabetes, and cancer (Ishii, 2015). Despite these genetic breakthroughs, questions are being raised over the negative implications that CRISPR will bring about concerning the permanent editing of the human genome and ultimately the course of human evolution. As a current college freshman, there is no doubt in my mind that I will witness the opening of this "genetic Pandora's Box" within my lifetime, but if the scientific community proceeds with moral caution, fueled by global debate and the implementation of global policy and guidelines, CRISPR can be used as a therapeutic and preventative technology rather than an enhancement and cosmetic tool. By looking at the past and present guidelines of genetics, we can safely shape the policies of the genetic future.

Background Information

Genetic Modification

Genetic modification is the all-encompassing term for editing a living organism's genetic information in a way that could not naturally occur via mating and reproduction. Genetic modification includes methods such as gene targeting, genome editing, and recombinant DNA, as well as the transfer of genetic material from one non-mating species to another, also known as horizontal gene transfer. Organisms such as cells, microbes, plants, and animals have long been used in genetic modifications and are classified as GMOs (Personal Genetics Education Project).

Somatic Gene Therapy vs. Germ-Line Engineering

What is the difference between somatic gene therapy and germ-line engineering, and what is so controversial about the applications of germ-line editing? Genetic engineering via somatic gene therapy includes the transfer of genetic information (DNA) to any cell in the body that does not produce sperm or eggs. Somatic gene therapy does not pass the individual's genetically modified cells onto its offspring (Yourgenome, 2016). Germ-line engineering on the other hand, includes the transfer of DNA to an individual's sperm and egg cells, resulting in the passing down of that individual's genetically modified cells to its offspring. Germ-line editing also known as genome editing, uses different methods for genetic modification including designable bacterial nucleases, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR (Ishii, 2015).

What is CRISPR-Cas9 technology?

CRISPR technology is designed to make a break at any target sequence chosen by the experimenter or doctor in order to modify the genetic makeup of that specified locus (Carroll & Charo, 2015). The "Cas9" enzyme allows for the targeting of multiple DNA sequences simultaneously because the protein can be mixed with more than one guide RNA due to the protein's uniform nature throughout the process (Benston, 2017). CRISPR-Cas9 innovations have been met with praise from the scientific community for its outstanding performance in speed, accuracy, ease of use, and low cost (Katz & Pitts, 2017).

Why We Should Edit the Human Genome

The biggest reason that CRISPR-Cas9 has reached celebrity status throughout the scientific community, is for its future applications in preventing the transmission of genetic diseases to one's offspring. CRISPR being used as a preventative medicine is likely to be suggested for subjects with congenital anomalies caused by chromosomal, monogenic, multifactorial or environmental/teratogenic factors. From these, monogenic diseases such as Huntington's and Cystic Fibrosis are likely to be treated in a clinical setting due to the need for just a small repair in one's genetic makeup (Araki & Ishii, 2014).

It is currently possible to diagnose life-threatening genetic, chromosomal, and or developmental diseases in a mother's fetus, however, selective abortion is one of the few options for parents looking to ensure their child the highest quality of life upon birth. The future of reproductive genetics looks to utilize the technology of CRISPR to decrease the number of selective abortions due to these potentially correctable life threatening genetic diseases (Singh, 2016). Children whose parents choose to forgo abortions, will become part of the statistic that

roughly 6% of all births have a serious genetic birth defect or a defect that is somehow genetic in origin. Gene editing techniques have the potential to eliminate these birth defects benefitting nearly 8 million children each year (Savulescu, Pugh, Douglas, & Gyngell, 2015). In addition to correcting immediate birth defects caused by genetic abnormalities, CRISPR has the potential to find and correct genetic defects that play a role in developing chronic diseases such as diabetes or cancer at a premature age (Savulescu, Pugh, Douglas, & Gyngell, 2015). As of now, those who are alarmed at the prospect of editing the human genome can breathe a sigh of relief as current techniques in various stages of clinical development focus on modifying the genetic material of somatic cells and are not designed to affect sperm or eggs (Lanphier, Urnov, Haecker, Werner, & Smolenski, 2015).

Ethics Against Editing the Human Genome

Many people from across the globe have argued that scientists should not be allowed to alter the human genome. They argue that editing the human genome questions the morality of human beings and the notion that we are God's creatures. Editing the human genome and ultimately enabling a child to one day pass those altered genes onto their children has ultimately been labeled by some as playing the "God card" and that human beings should just stick to the idea of letting evolution play out its role in our futures.

Like all new technologies, there is a potential for the development of unpredictable effects on future generations. This makes editing the human genome especially dangerous and ethically unacceptable. Research could also be exploited for non-therapeutic modifications. There is also a concern by many in the scientific community that a public outcry about such an

ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited (Lanphier, Urnov, Haecker, Werner, & Smolenski, 2015).

Monitoring the Future of Genetic Applications

Some of CRISPR-Cas9's potential applications have produced numerous problems questioning the morality and ethics of the controversial technology. Because of this, society will have to determine what our collective genetic morals will be, and how we should approach this new age of scientific discovery. Laws will be necessary to keep up with the rapid expansion of technology to decide whether we will alter the human genome for solely medical purposes or whether some will use it for cosmetic purposes as well (Ishii, 2015). The scientific community will likely continue to research the future clinical applications of CRISPR technologies, but some still worry that scientists will continue to further investigate the cosmetic enhancement applications of CRISPR creating multitudes of social, economic, ethical, and racial issues worldwide. To prevent scientific advancement from morphing into genetic enhancement, the global scientific community will have to come together to promote a public dialogue concerning the ethics and morals of CRISPR to continue research that will please the majority and create lasting change and awareness.

In order to slow the cosmetic enhancement applications of CRISPR-Cas 9 technologies, scientists, doctors, lawmakers, and the public from all across the globe will have to willingly discuss the global implementation of laws and guidelines in the scientific field to define and determine what the differences are between gene editing, gene therapy, germline engineering, designer babies, and CRISPR-Cas9 technology and how they challenge and shape our ethical values. Additionally, we should look at all the past and present legal standings world-wide and

decide if we can further build off those or if they need to be reexamined. By doing so we can carefully approach the future applications of CRISPR and germ-line engineering.

How the Abortion Debate Plays a Role

In the United States, gene editing technologically is growing rapidly unchecked by any sort of political or legal mechanisms (Tuhus-Dubrow, 2007). Many people as of late, have been quick to place the blame of unchecked scientific growth on the pro-choice and abortion rights movements in the United States because of the groups' century long battle calling for the reduction of government interference in the realm of reproductive rights. Advocates for reprogenetic technology and the pro-choice movement are finding that they are being increasingly associated together as one common movement since they both are involved in the politics of the future developments of the human embryo and what science wants to do with it. Some argue that to obtain the adequate funding necessary to provide the safe clinical practice of genetic editing for health purposes, the politics of abortion must be separated from the topic of human embryo research (Annas, Caplan, & Elias, 1996). People argue that when federal funding begins to be prohibited by the politics of abortion that no progress can be made into making the practices of embryo research morally and ethically appealing to the American society. The more funding there is for embryo research, the better safety procedures and technology can be provided to expecting mothers wishing to prevent the onset of genetic diseases in their genetic offspring (Annas, Caplan, & Elias, 1996). Despite the many overlappings between the federal funding of human embryo research versus the abortion debate, many agree that the two need to develop their morals separately from each other on the grounds that many people hold the moral idea that life begins at conception and embryos, despite being made up of human genetic

material, do not implant themselves into the uterine wall, and therefore cannot develop into adulthood (Annas, Caplan, & Elias, 1996). The separation of these two controversial topics is again essential for proper government funding for genetic research that will create safe clinical applications of genetic engineering while being complicit with ethical standards.

The History of Genetic Engineering Policies and the Role of Reproductive Rights

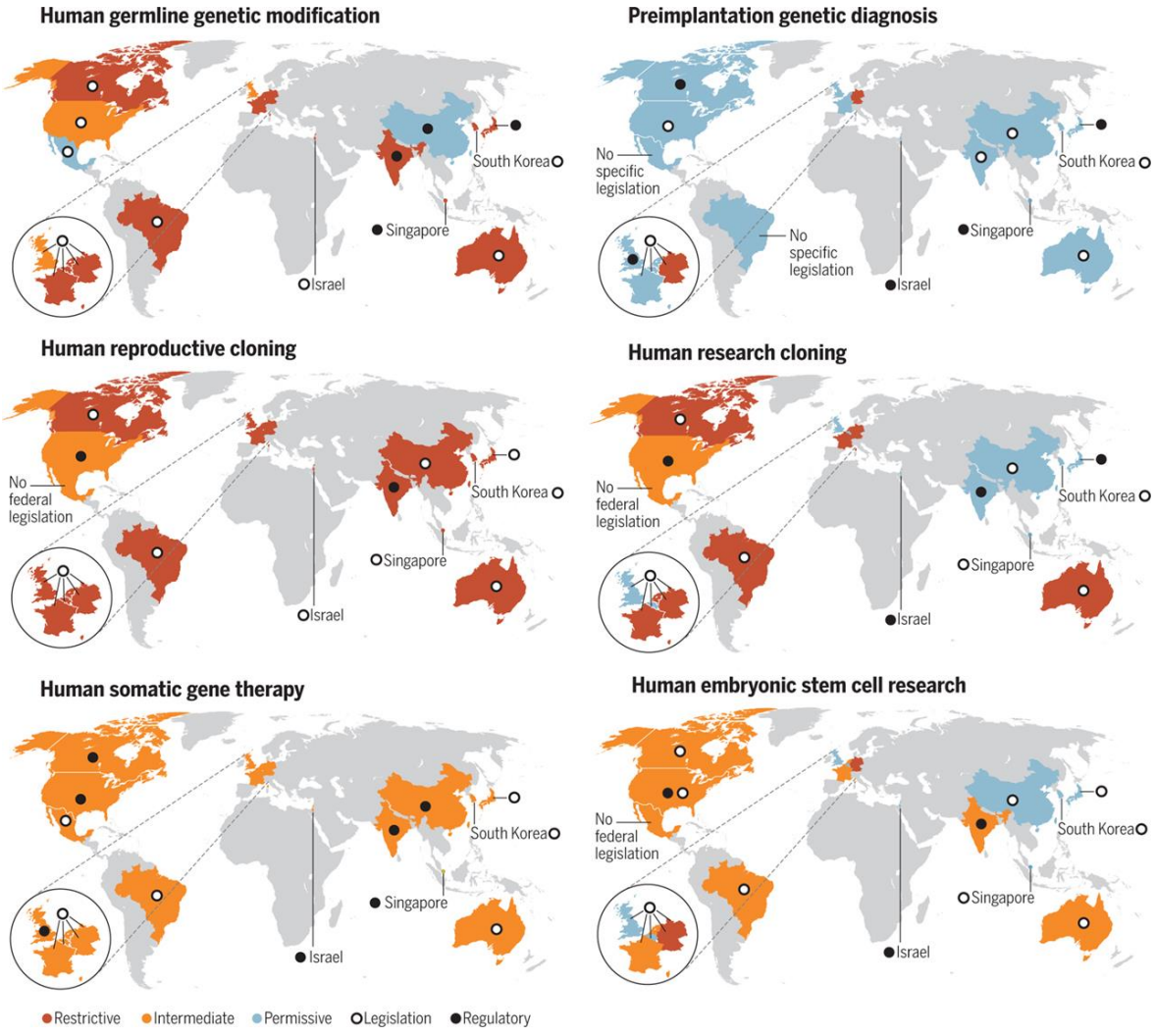
Despite the arguments calling for the independent growth of abortion rights and reprogenetic technology, there is no denying the fact that the future of genetic reproductive rights will grow out of the century long struggle of women fighting for the right to plan their families on their own terms. In order to predict what the future of reproductive rights will look like, we need to understand the history of reproductive law up to the present in order to determine how the current law will affect the future. The criminalization of abortion in the United States first began with the passing of the federal Comstock Act by U.S. Congress in 1873 (U.S. Congress, 1982). The Comstock Act was an "Act of the Suppression of Trade in, and Circulation of, Obscene Literature and Articles of Immoral Use," and although the act did not outlaw abortion in any sense, it did turn the idea of women seeking abortion into something of a medical taboo (Encyclopaedia Britannica, 2017). By the end of the 19th century almost all 50 states had to some effect laws banning abortions (Blakemore, 2018). The arrival of the eugenics craze pre-World War II brought with it the legalization of forced sterilization in the United States and many people today are beginning to wonder if genetic editing could bring about a second wave of "positive" eugenics. In the year 1927, the United States Supreme Court upheld in *Buck v. Bell (1927)* that according to the Virginia Code of Conduct, any inmate housed at a state institution suffering from idiocy, insanity, epilepsy, feeble-mindedness, or imbecility could be subject to

forced sterilization (Wolfe, 2015). Thankfully, the state of Virginia repealed the law in 1974. The current era of the pro-choice movement began with the infamous United States Supreme Court Case Roe v. Wade (1973). In the case, the court ruled 7-2 that states restricting abortion was unconstitutional on the grounds that it violated the Fourteenth Amendment's due process clause (Encyclopaedia Britannica, 2017). Exactly a century after the Comstock Act was enacted, the Roe v. Wade case, and the many cases that followed suit, paved the way for inhibiting governmental interference in reproductive rights. This is where advocates of increasing the governance of gene editing technology find major road blocks. So far, advocates for enhancement gene editing have pointed to Roe v. Wade and its handful of successors saying that governmental interference in gene engineering would be interfering with the reproductive wishes of the expectant mother. Ishii points out that countries with lax regulations, will inevitably offer the option for genome editing-mediated enhancement, but I think that we will also see this phenomenon begin to occur in countries like the U.S. where extreme reproductive regulations were oversimplified to allow for little governmental interference in the realm of reproductive rights (Ishii, 2015). Obviously, no one could have predicted that these huge strides forward in gene editing technology would begin to pit pro-choicers against reprogeneticists.

Current Genetic Policies

When looking at the international regulatory landscape encompassing the policy of germ-line engineering, one sees a vast mosaic of differing policies worldwide. Policies across the globe distinguish between degrees of permissiveness, between legally binding legislation and regulatory and or professional guidance or research versus clinical applications. Most countries worldwide either take a legislative approach in governing

genetic engineering or regulatory approach where genetics are governed by normative documents and policies. The figure below illustrates the spectrum of global policies for 16 representative countries regarding germline engineering, stem cell research, human cloning, human research cloning, somatic gene therapy, and pre-implementation genetic diagnosis. The figure also depicts countries where innovative research is occurring concerning stem cells and genomics and also includes any hot spots for stem cell and reproductive tourism (Isasi, Kleiderman, & Knoppers, 2016).



Legislative policy so far as resulted in either the prohibition or restriction of germline engineering and has been enacted in countries such as Australia, Canada, France, Germany, Brazil, Israel, and so on. Breach of policy can result in a range of punishments from small fines to long imprisonment time (Isasi, Kleiderman, & Knoppers, 2016).

Global restrictive policy also takes on germ-line engineering using upstream limitations using restrictions in a bottom-up sense, putting a ban on a broad range of genetics including human embryo and germline manipulations, somatic cell transfers, and even embryo genetic testing. This type of restrictive policy is most notably seen in Canada and Germany today.

Third, there are a few countries worldwide that aim to promote scientific research and progress taking a more permissive approach in governing research towards future germ-line editing applications. Such countries include China, and the United Kingdom, which until recently held a very conservative view on the potentials of editing the human genome (Isasi, Kleiderman, & Knoppers, 2016).

The United States

In the United States, genetically modified organisms such as GM crops, are subject to the most regulation under federal agencies. GM crops are regulated by the United States Department of Agriculture, Animal and Plant Health Inspection Service, and the US Food and Drug Administration. These crops may also be required to undergo public review under the National Environmental Policy Act, should federal agencies ask (Carroll & Charo, 2015).

Biotechnology in America is significantly less regulated when compared to the regulation of American GM crops. Current policy regulates products based on their intended uses and characteristics whereas crops are analyzed via their method of production (Charroll & Charo, 2015.) Additionally, the first CRISPR gene therapy protocol in the US was introduced and approved in the year 2016 (Lecuona, Casado, Marfany, Baroni, & Escarrabill, 2017).

Alarm has also been raised over the economic and profit morals that are likely to be tested in regard to CRISPR technology. The biggest example of this in the United States is the ongoing CRISPR-Cas9 patent dispute between the University of California, Berkley and the Broad Institute of MIT at Harvard. The commercialization of research has pitted these two great institutions against each other in the search for individual profit, despite the global history of universities coming together to foster a culture of scientific collaboration. It is becoming an increasingly common theme for academic institutions to take each other to court over patent disputes, which makes sense when looking at the potential billion-dollar price tag attached to the CRISPR-Cas9 patent. The two institutions could have avoided court by simply filing both research teams as co-inventors on the patent application but since the enactment of the Bayh-Dole Act in the year 1980, universities have since been able to garner federal funds by stating legal ownership over scientific property heightening the tension between institutions. UC Berkley and the Broad Institute are set to settle the patent dispute with the Federal Circuit Court of Appeals on April 30, 2018 (Sherkow, 2016).

Europe

Europe approaches genetic engineering with significantly more pre-market control than that of the United States. Genetic engineering is regulated less in the sense of potential product usage once on the market but more in the sense of the need for any special product requirements

such as product labeling or warnings. Europe acts increasingly more on the precautionary principle and encourages governmental authorities to prohibit and or compel commercial speech by there being fewer governmental limitations overall. (Charroll & Charo, 2015).

Led by the United Kingdom, The European Union has under gone debate regarding the bioethical applications of CRISPR-Cas9 technology. The EU recognizes not all cultures hold the same perspective on providing restrictions for the controversial technology and that is why encouraging debate is so important to the future of this technology.

In February 2016, a team of British researchers was given the first authorization to apply CRISPR technologies in leftover *in vitro* fertilization embryos by the British Human Fertilization and Embryology Authority (HFEA). This authorization allows for the applications of CRISPR in healthy embryos from newly formed to 7 days old, requiring their destruction after the latter (Lecuona, Casado, Marfany, Baroni, & or Escarrabill, 2017).

Asia

In a literature review study, studies of Japanese literature showed that Japan and Asian countries in general, are more positive towards gene technologies but are the most critical of pre-implantation genetic diagnostic (PGD) applications when compared to Western public literature and debates (Dijkstra & Schuijff, 2016). As a region, Asia is most likely to opt out of regulating biotechnology because many Asian countries are either non-democratic or lack constituencies that are strong enough to object to these morally questionable biotechnologies (Fukuyama, 2002).

The Future Genetic Political Landscape

Trying to create permanent legislation in the United States regarding human genetic modification has already proven to be difficult, and some argue that if we cannot even control the genetic advancements in the United States, then how will we ever come to a worldwide policy agreement? Some believe that the solution to this question lies in the idea of "harmonization." They define the phenomenon of international regulatory harmonization as seeking to have countries worldwide enforce similar legal requirements or regulations despite the inner-workings of that country's legal system (Marchant & Allenby, 2017). They cite medical tourism (when patients or scientists travel to another country in order to receive or investigate medical treatment outlawed in their home country) and the trans-national applications of CRISPR technology as the two biggest calls to harmonize internationally but countries can't adopt forms of "hard laws" such as treaties, and legislation as they have done in the past (Marchant & Allenby, 2017). Instead, they suggest the use of the "soft law," defined as arrangements creating global expectations that are not directly enforceable like say, a treaty or a statute, but, nevertheless are an important instrument in enforcing intergovernmental regulation of human gene editing (Marchant & Allenby. 2017). Examples of international "soft laws" that would hold the potential of regulating the international playing field are types of private standards, guidelines, codes of conduct, and principles. They argue that although these methods hold no direct level of government enforcement, that things such as the ethical standards of professional societies or even say international insurance contracts with researchers will be able to enforce a certain kind of global moral compliance (Marchant & Allenby, 2017). One of the biggest benefits of using the technique of "soft law" global governance is that unlike a legal treaty document for example, which is hard to change out of the aspect that a treaty is a legal

document spanning multiple international actors. “Soft laws” are flexible. Their informal structure makes them easier to modify in response to the changing technological and international landscape.

It is important that nations around the world encourage global discussion and debate regarding the future of germline engineering. The International Summit on Human Gene Editing held in Washington, D.C. in December 2015 was a 3-day event encouraging the exploration of the many questions surrounding the use of gene editing tools in humans. After 3 days of deliberation, the summit concluded the conference by encouraging the governance of global human gene editing. They encouraged not only the political governance of gene editing but also the governance by the private industry, research and educational institutions, advocacy groups, as well as professional societies (Committee on Science, Technology, and Law Policy and Global Affairs, 2015).

While it is important to hear the professional opinions concerning the future of human genetic policy, it is also important to hear from the young people that are likely to be affected by this technology in the future. A study done in 2004 in Southern Wales asked the opinions of a citizens’ jury of young people on various topics concerning designer babies. In regard to regulation, all young people expressed support for some form of regulatory system in the United Kingdom (Iredale, 2006).

Conclusion

The possibility of being able to edit the human germ-line via CRISPR-Cas9 technologies has brought about a wave of both public and scientific excitement and fear over the numerous possible applications of the controversial technology in the realm of the medical field and

beyond. In order to prevent any morally questionable uses of the CRISPR-Cas9 technology, national and global policies will have to be implemented drawing from global debate and discussion that engages both the scientific community and the public in taking part in shaping the course of human evolution.

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