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The CRISPR-Cas9 mediated disruption in the ethics of gene therapy: an analysis of contemporary developments

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The CRISPR-Cas9 Mediated Disruption in the Ethics of Gene Therapy: An analysis of contemporary developments

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Introduction

CRISPR-Cas9 can shift the ethics of gene therapy

The discovery of the CRISPR system in many ways epitomizes the rewards of genuine scientific curiosity to understand natural phenomena. What turned out to be CRISPR was, at the time, nothing more than repeating patterns in the genome of bacteria and in this context presented no fame, money, or prestige. However, what was born out of the understanding for the mechanism that generated these repeating patterns is now responsible for a growing excitement in the scientific community and has become anything but humble. Unlike its origin.

CRISPR, in its essence, is nothing more than a bacterial immune system that, when combined with the Cas9 enzyme, becomes a powerful and effective tool to edit genomes in eukaryotic cells. Since the genome is the fundamental blueprint of living organisms, harnessing this power presents the ability to alter very specific traits that seem to be limited only by our creative potential.

Its use since 2012, when it was first developed into a gene editing tool, has had far reaching impacts on research, and is now finding its way into use on humans. Said uses have so far been limited to research on its medicinal use via gene therapy. Even though CRISPR-Cas9 presents a tremendous upside by offering cures to genetic illnesses, there has been reluctance to adopt its use. This is because the use of CRISPR-Cas9 on humans brings up new questions of science and progress that are unprecedented: questions such as how to balance the risks and

benefits of CRISPR, or even to what extent should we use technology to modify life when such modifications are made possible.

These questions represent matters that can have a profound effect throughout society and in life. It is therefore imperative to realize that progress for the mere sake of progress is something that can lead to very dangerous outcomes and there must be regulation to prevent such outcomes from occurring. Because the use of CRISPR-Cas9 on humans falls into the realm of gene therapy, regulation of its use on human bodies has thankfully already been established the creation of gene therapy. The important nuance to this, however, is that these regulations are not "set in stone".

This highlights an important trend in bioethics because it has become a means of regulating the social acceptability of newly emerging technological possibilities and implies that there is an underlying relationship between technology and society. Since the regulations on gene therapy stem from bioethics, the implications of this relationship are massive as it suggests that CRISPR-Cas9 possesses the agency required to incite change in the ethics/ regulatory framework of gene therapy. Further, as CRISPR-Cas9 gene editing advances by becoming increasingly accurate and cheap, it is also becoming increasingly apparent that it will cause a shift in the ethics of gene therapy. To explain how this occurs, I must first emphasize the impact of CRISPR-Cas9 on gene therapy and highlight specific points where it can change the ethics of it.

When gene therapy was first postulated, it generated much excitement due to the possibilities for fighting many genetically linked illnesses. Unfortunately, success was elusive as gene therapy failed to live up to its initial expectations as it was demonstrated to be very expensive as well as dangerous. Not surprisingly, much of the excitement wore off. However, gene therapy continued to present an upside insofar that it gave way to the possibility of gene

editing, which was beginning to be fulfilled through the development of zinc finger nucleases (ZFN) and transcription activator-like effector nucleases (TALENs). While these technologies are still in use, the emergence of CRISPR-Cas9 presents a disruption in the use of gene therapy.

By tracing the development of gene therapy research using CRISPR-Cas9 since 2012, I have observed a pattern of its increasing infringing upon the bios. If this pattern continues, the use of CRISPR-Cas9 for gene therapy will eventually collide with established ethics. This, in turn, will force their reevaluation. To suggest that this is the case, I will focus on two current restrictions that CRISPR-Cas9 is likely to have an impact on: the ban on germline manipulation and limits to the medicinal application of gene editing.

This is mainly due to questions regarding the safety of using CRISPR-Cas9 since the long-term effects have yet to be fully evaluated, and some scientists have called for a moratorium. Interestingly, this response parallels that of the early use of DNA recombinase technology which has since grown considerably and is becoming increasingly normalized in society today. It is through this normalization where the shift in ethics regarding germline manipulation and accessibility can occur, driven by biopolitical forces that constitute both a will and a means for normalization.

This interaction provides the framework for my thesis, in which my aim is to suggest *the bioethics of gene therapy will shift by the rise of CRISPR-Cas9 gene editing*. To do so, I will explain how shifts in the bioethics of gene therapy are occurring through contemporary CRISPR-Cas9 research. Further, this will be done by outlining the biopolitical forces driving shifts in bioethics and how they serve as a mechanism for shifting the ethics/regulations of contemporary gene therapy. I hope that it will serve to both highlight how far we have come, and, based on this trajectory, what can come next vis-à-vis the ethics of gene therapy and its use on humans.

Chapter One:

Contextualizing CRISPR-Cas9 in Gene Therapy

Few discoveries can redefine our fundamental understanding of nature and change the course of humanity. When in 1868 a young Friedrich Miescher looked microscopically into the pus of discarded surgical bandages and discovered a new molecule (aptly named *nuclein)* (Dahm, 2008), little did he know that he was staring at such a discovery. Years later, nuclein's capability was realized when Hershey and Chase confirmed that it (now known as DNA) was the carrier of genetic material and a year later the now famous Watson and Crick solved its structure with the aid of Rosalind Franklin and Maurice Wilkins. For the first time in human history, we could finally metaphorically stare into the eyes of God by understanding how we are created. What truly made this discovery change humanity however, is the development of technologies stemming from the understanding of DNA and its role in building proteins unique to every species. Doing so is allowing us to influence the very essence of that makes living organisms what they are through genetic modification.

To understand this influence, one must first understand the background of genetic modification and its interaction with society. Genetic modification is nothing new. Despite a lack of understanding of genetics, humans have influenced the phenotypes of other organisms for around 32,000 years. In East Asia, wolves were selected to become more submissive which eventually led to the selection of certain traits to give us modern dog breeds (Wang, Guo-dong, et al., 2012). In ancient Mexico, kernels from particularly large and perhaps better tasting

teosinte grass were selectively planted, resulting in progressively larger teosinte which displayed more rows of kernel and eventually become known as maize (Doebley, John, et al., 1990).

It would be thousands of years until Darwin's *The Origin of Species* brought about an understanding of evolution and subsequently artificial selection. This understanding, alongside that of Gregor Mendel's concept of heredity redefined our understanding of humanity's place in nature. In other words, where previously our understanding of where organisms originated rested on creationist ideology, a paradigm shift occurred giving humanity a newfound agency as it now believed that it was a part of nature (Berra, 2008). With this newfound agency, research would shift to the dominant paradigm and proceed into what Kuhn called a "normal science" (Kuhn, 2012). Within normal science said research was done and continues to be done through a puzzle-solving framework that aims to further understand and explain heredity, leading to the discovery and further understanding of DNA's role in heredity.

The process of furthering this understanding also allowed for the development of new technologies. In the early 1970's, this development was manifested with the creation of direct DNA manipulation through genetic recombinant techniques. Its earliest use created the first transgenic organism by inserting antibiotic resistance genes into the plasmid of an *E. coli* bacterium (Cohen & Chang., 1973). The relative success of this work set the precedent for future genetic modification, however, despite the opportunities recombination technology presented, the environmental and public health risks were uncertain, hence society was hesitant to adopt its use. An example of this is the use of SV 40, which was known to cause cancer in rodents and thus, there was the fear human cell cultures which underwent SV 40 recombination could break out and cause cancer (Berg, 2008).

Risks such as those posed by SV 40 as well as the fear of additional unknown risks led scientists to sound the alarm and called for a global moratorium on the use of DNA recombination. However, the moratorium was never implemented and instead the reservations of scientists led to a conference in 1975 held at Asilomar to set standards that had both public health and research interests in mind. This now famous conference set forth early standards and safety guidelines for work with recombinant DNA.

Further, the decisions and guidelines laid out at the Asilomar conference also increased public interest in genetic modification, which has been attributed for kick starting the biotechnical industry (Wright, 1986) that increasingly sought out ways to apply genetic modification to medicine. Because of this push, gene therapy, which aims to replace or disrupt defective genes, was born in the early 1990's. The first use of gene therapy was used to treat four-year old girl Ashanti DeSilva who suffered from ADA-SCID (Blaese., et al., 1995). A few years later, cancer gene therapy was introduced (Trojan., et al. 1993), and new vectors were used to deliver genes (Abbott, 1992). This was cause for a lot of excitement as it opened a lot of treatment options for many previously incurable illnesses. For a short period during this time, it appeared as if a new paradigm[4] in medicine was in order.

Unfortunately, gene therapy did not live up its potential. Obtaining lasting effects was difficult, if not impossible in early trials, and the community quickly grew skeptical (Friedman, 1996). Then, the 1999 gene therapy related death of Jesse Gelsinger signaled a warning sign to the American scientific community, which responded by suspending several trials. Further, in 2003 this skepticism was additionally soured when reports from Paris announced that several

[4] The use of the word "paradigm" in this case is does not apply to the Kuhnian definition because it applies strictly to technology. Rather, here it is used to show that beliefs regarding gene therapy as an application to medicine were widespread.

gene-therapy patients developed leukemia, leading to one death. Despite subsequent reports of successful gene therapy, there remained a sense of doom around the issue and gene therapy was now at a dead end.

Returning to the puzzle-solving framework described above, the new paradigm of gene therapy presented different ways of delivering genes. Where the first technology was focused on activating certain proteins that led to failures which the increased pessimism of gene therapy, technology progressed to enable the actual editing of genes themselves. This development has so far created technologies such as gene editing technologies such as ZFN and TALENs. However, the very recent development of CRISPR-Cas9 has/is creating a lot more excitement than the former due to its potential to edit genes much more effectively and cheaply. To understand why this is, and what makes CRISPR-Cas9 such a powerful gene editing tool, it is imperative to understand how the technology works.

Despite often being viewed as a single entity, CRISPR-Cas9 is an interaction between the CRISPR loci and its Cas9 effector enzyme. Clustered regularly interspaced short palindromic repeats (more commonly referred to as CRISPRs) serve as an adaptive immune system for bacteria against infections (Mojica, et al., 2005). They are broken up into two different classes, class I contains multi-subunit effectors while class II contains single protein effectors. Within these classes are five different subtypes, CRISPR-Cas9's being class II type II (Lander, 2016), due to differences in individual types, only the pathway of type II immunity is described below[1].

[1] It is interesting to note that there are many different types of CRISPRs, however, because the scientific focus lies largely on the CRISPR-Cas9 mechanism for gene editing (as opposed to working with other CRISPR systems) warrants some consideration as to how this push can be socially constructed through actor network theory.

CRISPR immunity works in three different stages which work to break down invading DNA:

(1) acquisition, (2) crRNA processing, and (3) interference.

1. Acquisition begins with the recognition of invading DNA (such as a bacteriophage) by the Cas1 and Cas2 enzymes, leading to the cleavage of a protospacer. The protospacer then is ligated to the direct repeat adjacent to the leader sequence and single strand extension repairs the CRISPR and duplicates the direct repeat. The primary CRISPR transcript is cleaved by Cas genes to produce crRNAs (Swarts et al., 2012).

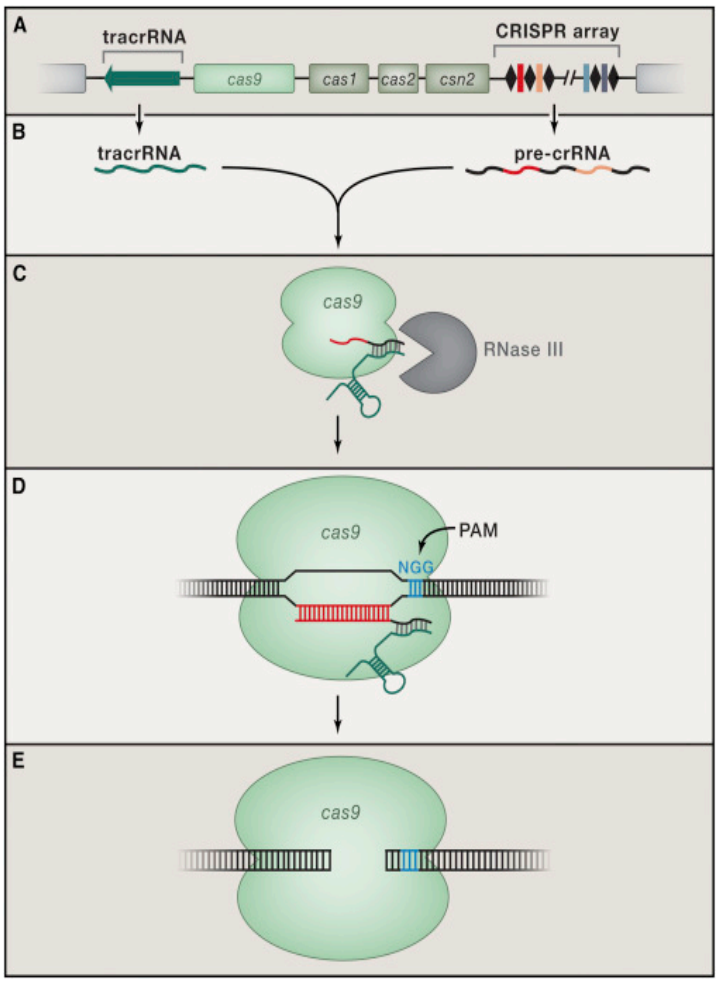
2. crRNA processing in type II systems involves the use of trans-activating (tracr) RNA to form dsRNA, which is cleaved by Cas9 and RNaseIII. Secondary trimming is then performed at either the 5' or 3' end which produces mature crRNAs. These mature crRNA associate with Cas proteins to form interference complexes.

3. Interference is caused by the resulting complex (Cas9 + tracrRNA + crRNA) which locates the DNA sequences that match the spacer sequence and binds to the target site with the help of PAM. Once Cas9 binds to a target site with a match between the crRNA and the target DNA, it cleaves the DNA three bases upstream of the PAM site (Lander., 2016).

The image below[2] both illustrates and summarizes the class II, type II CRISPR-Cas9 system[3].

[2] This image was originally published in Vol. 164 p. 19 of *Cell* in the article "The Heroes of CRISPR" by Eric S. Lander

[3] From this image, it is important to notice that in the last step, the cleavage site creates two blunt ends because this gap can be manipulated to be filled by an artificial sequence, which gives CRISPR-Cas9 the ability to edit genes



The use of the CRISPR associated (Cas9) protein is critical in type II CRISPR immunity as it is the only known effector for this type. This is due to its unique structure which allows it to locate and cleave target DNA with high accuracy and efficiency. Its structure is broken up into six domains: REC I, REC II (role not well understood), the Bridge Helix, the PAM interacting domain, HNH and RUVC. REC I is responsible for binding to the guide sequence, while the bridge helix initiates cleavage activity upon binding on the it. The PAM interacting domain confers PAM specificity, making it responsible for initiating binding to target DNA. The HNH and RUVC domains cut the single-stranded DNA. (Nishimasu et al. 2014).

What gives CRISPR-Cas9 the ability to edit genes relies on the fact that the Cas9 can be activated with an artificial guide sequence which targets a specific area. This activates the second stage of the CRISPR system in which the Cas9 enzyme locates the matching protospacer adjacent motif (PAM) sequence and cleaves it which leaves a gap in the genome. This gap can then be filled by an artificial repair template that can be tailored to suit a specific need (such as fixing an SNP) by taking advantage of the cell's natural HDR process. Since this can be done on purpose and any desired sequence can be inserted into the target area, this technology gives us the power to edit virtually any genome. Additionally, this replacement becomes part of a cells genetic material, it is permanent. Therefore, it will pass into its daughter cells which gives CRISPR-Cas9 the ability to be used in gene therapy as a means of correcting genetic errors as well as preventing them from being passed on.

Nevertheless, there is an important caveat. CRISPR-Cas9 technology is by no means perfect, which can result in poor editing rates. Yet, since the discovery of CRISPR-Cas9 as a gene editing tool, these rates have decreased based on new advances. Said advances mainly come from the development of new ways to deliver the essential CRISPR machinery, namely through the recent use of ribonucleotide particles (RNP) which have been found to enable the highest editing efficiencies thus far. (Liang, X., et al., 2015) Further, the development of synthetic guide RNA (sgRNA) has added to this efficiency when combined with RNPs as researchers have consistently achieved a 90% efficiency.

The following image[4] helps contextualize the extent of the advances made in using CRISPR-Cas9 technology:

	Synthetic Guide RNA	Plasmid	IVT
Process	1. Choose target sequence 2. Order synthetic RNA	1. Choose target sequence 2. Design/order DNA primers 3. PCR insert 4. Ligate into plasmid 5. Transform into cells 6. Screen cells 7. Sequence verify plasmid 8. Purify plasmid DNA	1. Choose target sequence 2. Design/order DNA primers 3. Assemble guide by PCR 4. Perform IVT 5. Purify guide RNA
Time to Transfection	Ready for transfection	7-14 days	1-3 days
Transfection Labor Time	Minimal	Days of lab work	Full day of lab work
Off-target Effects	Lowest	Variable	Variable
Efficiency	Up to 90% efficiency	Variable	Variable
Consistency	Highest	Variable	Variable

As can be observed in the chart, the comparison between the different technologies and their corresponding efficiencies shows that recent technological developments are not only more efficient in terms of gene editing, but also increase productivity in the experimental process itself. This is done by reducing the time and cost required to use CRISPR-Cas9. In addition, the simplicity of the type II CRISPR system that I have described above gives CRISPR-Cas9 gene editing a lot of potential in the field of gene therapy because of how easily it can be used.

If this is the case, and if anything, the increased involvement from the private sector (Berg, 2008) strengthens the argument that it will, then the use of CRISPR-Cas9 for gene therapy on

[4] Adapted from *CRISPR 101* by the Synthego Corporation available for download online at: http://powered.synthego.com/crispr-101

humans will become more prevalent. This is because the potential monetary and medicinal benefits will lead to further development, which will make the technology safe for human use. Doing so will likely signal a new era in molecular biology and gene therapy as CRISPR-Cas9 technologies will continue to be used and become increasingly normalized in society.

Without a doubt, this new era in molecular biology will run into a plethora of ethical issues. However, ethics are a social construct and are therefore malleable. Naturally, this begs the question of how CRISPR-Cas9 can become normalized in contemporary society and subsequently affect the contemporary ethics of human germline manipulation. The answers to this question will be addressed throughout the remainder of this thesis.

Chapter Two:

The contemporary ethical frameworks behind gene therapy and the bio-political background for their disruption via CRISPR-Cas9 technology

The age-old question: "Just because we can, should we?" embodies the thoughts which can naturally arise when one thinks of gene therapy. After all, the ability to manipulate one's genome contravenes the boundary between man and nature. Doing so makes it more difficult to know what exactly is natural and how it can be distinguished from what is artificial. After all, these boundaries remained unquestioned since they laid well beyond our capabilities. However, this has since changed with the increase in biotechnology and therefore these existential questions are becoming increasingly relevant as technology advances and further disrupts this boundary.

These questions began to arise in the 1970's, when DNA recombination became available. According to Thomas Lemke, it became necessary for society to respond by regulating which processes were acceptable and under what conditions in addition to clarifying what kind of research would be prohibited (Lemke, 2011, p.26). This act is epitomized by the Asilomar Conference, where scientists, journalists, and policy makers got together to decide on such regulation. Among these, I am highlighting both of the following recommendations because they highlight the balance between both research and public health safety that was the key message from Asilomar[5]:

[2] To see the complete guidelines from the Asilomar Conference, please see:

- Containment should be made an essential consideration in the experimental design and should match the estimated risk as closely as possible.
- Government oversight is recommended until the technology is deemed safe

By balancing the interests of both public safety and research, the Asilomar Conference also set an important precedent about how a proper response to new scientific knowledge was to develop guidelines that governed how to regulate it (Berg & Singer, 1995).

The increased public engagement from the conference also had a side effect by bringing about private interest in genetic engineering and escalated the amount of progress made in the field (Berg, 2008). These advancements only further infringed upon the boundary as developments in gene therapy began to take place in the late 1980's. Hence, the regulations Asilomar established only served as a Band-Aid because gene therapy raised a new range of ethical concerns due to the use of genetic modification on *humans* as opposed to non-human organisms.

Of primary concern were the issues of the safety of the patient as well as the accessibility of gene therapy with regards to who could use it/ what should be treated. Thus, a second conference was held in 1990, this time focused on the ethics and human values regarding genetic screening and therapy. This conference produced the Declaration of Inuyama[6] which established

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Berg, P., Baltimore, D., Brenner, S., Roblin, R. O., & Singer, M. F. (1975). Asilomar conference on recombinant DNA molecules. *Science*, *188*(4192), 991-994.

[6] The full text for the Declaration of Inuyama is available in appendix A and was obtained online from The Council for International Organizations of Medical Sciences (CIOMS), in official association with the World Health Organization (WHO). A copy is also available online at: http://www.cioms.ch/publications/guidelines/1990_texts_of_guidelines.htm

regulations and gave recommendations for the future use of gene therapy.[7] While the creation of this declaration was an inherently political act, the considerations it placed on the regulation of gene therapy are naturally situated closely to the concerns of bioethics. This is simply because the act of creating such regulation on "the *social* acceptability of what is technologically possible" (Lemke p.26), touches on essence of what ethics are: moral principles that govern a *group's* behavior.

With this in mind, it is imperative to understand that regulation regarding the use of gene therapy then simply becomes the product of several ethical frameworks that are largely informed by sociological thought. Said frameworks are prevalent throughout the declaration of Inuyama and consist of utilitarianism, Kantianism and liberalism.

Utilitarian and Kantian Ethics

Germline gene therapy would specifically target human reproductive cells. As such, any modification made to these cells would be passed down to future generations. This would allow the correction of harmful genetic variations that have been passed down throughout human existence and spare future generations from the disease (Anderson, 1989). However, section VI of the Declaration of Inuyama states "The modification of human germ cells for therapeutic or preventive purposes would be technically much more difficult than that of somatic cells and is not at present in prospect. Such therapy might, however, be the only means of treating certain conditions, so continued discussion of both its technical and its ethical aspects is essential.

[7] While there have been other similar conferences since then (i.e. the 2016 Summit of Human Gene Editing), they have largely reinforced the regulations established by Inuyama which makes Inuyama central to discussions on the ethics of gene therapy.

Before germ-line therapy is undertaken, its safety must be very well established, since changes in germ cells would affect the descendants of patients" [8]. Hence, germline modifications are currently banned[9]. As such, any U.S. public funding into this research is not allowed[10] which has manifested itself through an NIH prohibition on research using gene-editing technologies in the human germline citing "ethical concerns" (Collins, 2015).

From the text, it is clear that the future use of germline modification is feasible, however, ultimately the safety issues are of concern which led to the ban on its use. This is the clear work of both utilitarian and Kantian ethics; since the prohibition is a product of both more difficult techniques which would require more resources (and hence lack utility) as well as a moral (and therefore Kantian) opposition to subject future generations to potential danger.

In terms of utilitarian ethics, which focuses on maximizing utility, the amount of research required to produce technology that enabled safe germline manipulation before the advent of CRISPR-Cas9 would have been very costly compared to the limited number of lives that could be saved. Therefore, allocating funds to create such techniques would greatly violate a foundation on utility. This is due to two factors, firstly, gene therapy techniques are mainly focused on treating illnesses that are caused by a single defective gene, which limits the population that it can treat. Secondly, such funding could better serve people suffering from genetic disease if invested in another way such as in-vitro fertilization (IVF) or genetic screening as this could also limit the spread of said disease to future generations.

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[8] Refer to appendix A

[9] For a list (last updated August 2014) of countries banning germline editing, please see:
Ishii, T. (2014). Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. *Reproductive biomedicine online*, *29*(2), 150-155.

[10] Part §46.124 of the United States Code of Federal Regulations

It is interesting to note that while prohibiting germline gene therapy under current conditions due to "ethical concerns" (Collins, 2015), section VI[11] also makes a rather vague case to continue the technical discussions regarding future use. This presents an oxymoron since research on the subject matter cannot receive funding from the U.S government, and seeking outside funding was difficult due to the similar standards set by the Declaration of Helsinki (Riis, P. 1977), hence this limited any possible (and very expensive) research to be funded by entirely private sources. Therefore, official progress in germline gene therapy under these restrictions could not be made. However, this does not account for alternative technologies that can become normalized overtime and modified to fit this purpose, as is potentially the case for CRISPR-Cas9. In this case, utilitarian ethics can very well shift as this use of technology suddenly presents greater utility than current alternatives.

Ultimately, the safety issue presented in section VI of the Declaration of Inuyama is clearly underscored based on the premise that the impact of germline manipulation is carried forward through generations, as can potential errors. Thus, when this policy was made, those in charge placed a heavy weight on Kantian ethics, since this ethical framework accounts for the basis of morality through the categorical imperative. In other words, in Kantian ethics, all rational beings (i.e. humans) can never be treated as means to an end, and as such it is morally obligatory that they be treated as an end (Kant, 1775).

In the case of medical ethics (in which gene therapy falls under) this morality is rooted upon the premise that all humans should have the right to dignity and respect. Applied further, this ethical framework makes it imperative that patients (such as those undergoing gene therapy)

[11] Refer to appendix A

are treated as treated as rational and moral people (an end) and thus should never be used to the benefit of society (a mean) (Sugarman & Sulmasy, 2010).

This moral theory serves as the basis for the safety clause in the Declaration of Inuyama by emphasizing that those who undergo gene therapy be treated as an end. Because germline manipulation has not been well established and thus its impact on both the patient and future generations is unknown, it cannot possibly be an end. Instead, it would lead to disregard of patient and their offspring's safety in the name of progress, which is in violation of Kantian ethics.

Liberal Ethics

Aside from the prohibition on germline manipulation in gene therapy, another key ruling is found in the Declaration of Inuyama is the accessibility of gene therapy. This is done by establishing regulation as to who can be treated. Section V affirms that "… Interventions should be limited to conditions that cause significant disability and not employed merely to enhance or suppress cosmetic, behavioral or cognitive characteristics unrelated to any recognized human disease". By limiting use to treat only those who suffer from a genetic disease, this clause essentially deters any potential misuse related to enhancement. While the reasons behind this are not explicit in the declaration, since it was written there have been many ethical arguments made about genetic enhancement[12].

These arguments generally boil down to the viability of genetic enhancement as well as its social impact. For the former, the viability is mainly the result of the limitations of being able

[12] A summary of these arguments can be found in:
Baylis, F., & Robert, J. S. (2004). The inevitability of genetic enhancement technologies. *Bioethics*, 18(1), 1-26.

to edit more than a few genes at a time and thus genetic enhancement would be difficult given that more than a few genes would need to be altered[13]. For the latter, the social impact of enhancement technology could freeze upward mobility within a nation (Mehlman, 1999) and globally further divide the gap between rich and poor countries.

The reasoning for this argument is that gene therapy can be very costly as is evidenced by the staggering record price of Glybera, which was marketed at a price of $1 million dollars to treat lipoprotein lipase deficiency (Morrison, 2015). Naturally, these high costs marginalize the poor and subsequently wealthier nations are better equipped to use gene therapy on their citizens, which could ostracize citizens in poorer countries. This issue is elegantly summarized by David Shenk in a 1997 essay in *Harper Magazine* when he pronounces that "…the social advantage that wealthy societies currently maintain could be converted into a genetic advantage. And the already wide gap between wealthy and poor nations could widen further and further with each generation until all common heritage is gone. A severed humanity could very well be the ultimate legacy of unfettered global capitalism" (Shenk, 1997). While Shenk's article was written years after the Declaration of Inuyama, the issues were clearly considered. This is evidenced by Sec. V which bans enhancement as well as Sec. VIII which stresses that the needs of developing countries be considered so they obtain a fair share of benefits (from the human genome project) such as gene therapy.

Given this context, the framers of the Declaration of Inuyama certainly placed a high value on the ethical principle of liberalism by pushing for equality since equality of access is an ideal. After all, the intention of limiting the influence of money on gene therapy provides more opportunity to everybody to receive treatment that is necessary. Furthermore, by emphasizing

[13] See utilitarian ethics section

liberal ethics, the Declaration of Inuyama fosters the spirit of globalization. This underscores the message that gene therapy is truly a global pursuit and as such, such technology could have an impact on everybody's life which is why access is important.

The Declaration of Inuyama

By looking at the situation leading to the Declaration of Inuyama itself, it must be realized that this was both a political act as well as a response to concerns that had never come up before. This suggests that certain ethical considerations had to be balanced over others, and that the people who formed the Declaration of Inuyama are the sole decision makers that weighed these issues to establish the ethics of gene therapy. In this case, there were 102 participants from 24 countries representing all continents. Their fields of expertise ranged from biomedical science to sociology, law, social policy, philosophy. They also brought in relevant experience in hospital and public health medicine, universities and private industry, and the executive and legislative branches of government. Because they came about a broad agreement, it is a safe assumption that their views embody the general perspectives of the world.

Based on these demographics, the feedback was given by a relatively diverse range of specialists in their fields as well as geographic makeup. Given this, the ethical frameworks which were given priority and mentioned above come to no surprise. What is worth noting about this however, is that while the World Health organization and the United Nations sponsored the event, there is no official enforcement agency. Hence, the Declaration of Inuyama is merely an agreement from those present to uphold these standards. As such, each entity is tasked with following the declaration based on their own independent agencies such as the internal review

board (IRB) or the FDA in the United States. This leaves room for individual interpretation, which can influence how countries regulate future technology.

Further, the Declaration of Inuyama was more than *just* politics. According to Thomas Lemke, interpreting such an act as traditional politics in incomplete, since biotechnology both encompasses the political subject and presumes that the political sphere remains untouched by growing technological possibilities (Lemke, 2011, p.30). Because these growing technological possibilities can at times further interrupt the boundary between man and nature, reevaluating previous regulations is practical based upon newfound understandings.

The development of CRISPR-Cas9 into a gene editing tool (Jinek et al, 2012), presents such a case. With the potential power for man to change the blueprint of cells, CRISPR-Cas9 is again forcing us to reestablish this border. In regards to gene therapy, this technology is appearing to become more accurate (and therefore safer) in successfully editing genes with the advent of synthetic guide RNA (Synthego, 2015). Surely if this progress continues, then we will be forced to revisit Inuyama since many of the regulations are premised by the lack of safe technology. After all, the improved safety of CRISPR-Cas9 has the potential to make its adaptation into gene therapy ethically feasible as noted above.

The impact of CRISPR-Cas9 would certainly force an update on the regulations of gene therapy if it were to be implemented. Ethics are ultimately just social constructs, and because the regulations behind gene therapy are based on them, any change could have a profound change on regulation. However, this does not mean that the Declaration of Inuyama should become obsolete since the balance of ethical perspectives established by it can be used to inform future policy by serving as precedents. If this is the case, then the use of CRISPR-Cas9 to modify the

germline can occur given both the lack of universal enforcement of regulations as well as by giving rise to a new interpretation of these ethical frameworks.

Because the boundary between man and nature is consistently shifting and needing to be reestablished, the altering of these regulations is not only possible but also justifiable. As such, in accordance with current ethical standards, any application of this technology should be restricted to somatic cells, at least at first. Yet if we refer to the precedents set forth by both the Declaration of Inuyama and the International Summit on Human Gene Editing, there is a very real possibility of CRISPR-Cas9 being used to edit the human germline. After all this technology is not only the cheapest and most effective way to edit the genome, it is also becoming increasingly safer and there is a large push for more research; both of the latter suggesting that CRISPR-Cas9 follows up on the preceding standards which allow for germline manipulation. This again leads us to the question: Just because we can, should we?

Chapter Three:

The will and the means: How can the normalization of CRISPR-Cas9 undermine current regulation in gene therapy?

What does a stone cutting tool have in common with a high-pressure water jet cutter? The obvious answer is that they can both cut an object; but other than that, there are little similarities in terms of accuracy, precision, time, and even what materials can be cut. When we look a little deeper, however, we see that both are constructed based on our fundamental understanding of nature in the context of history. Hence, when I paraphrase Martin Heidegger's *The Question Concerning Technology* by saying that technology is merely the application of science (Heidegger, 1977), this should come to no surprise. Continuing this line of logic, since science is a social construct, then the technology it produces is socially constructed as well.

Technology is not concrete and therefore is subject to change or even disappear based on how society views its application. Thus, throughout time, the technologies that tend to stick have become a part of a societal norm; suggesting that there is a certain political aspect to its application for it to be normalized. Returning to the cutting tool example, assuming the stone cutting tool was an early predecessor to the many modern cutting tools (such as the water jet), how did this technology evolve so much? The answer is that it likely was a product of a fundamental need in society to accurately split something, and because the tool could fulfill said role, its application was normalized, leading to its continued advancement. This illustrates what

Langdon Winner argues, that it is not the tool itself which is an object of politics, but rather its use and application (Winner, 1980).

The emergence of CRISPR-Cas9 gene editing technology as well as its potential for use in gene therapy falls well into this political framework. After all, the use of this technology must be able to fall in line with established societal standards so that it can become normalized. However, given the unique aspect CRISPR-Cas9 has as a biotechnology which has a direct impact on life, it also falls under the special realm of biopolitics. When life itself becomes politicized, the consequences are felt to the very core as the foundations, tools and goals of political action can shift (Lemke, 2011). Because of a shift in political action, bioethics, which are closely related to the changing biopolitics (Lemke, 2011, p. 26) can change as well. Herein lies the biggest issue and leads back to the question asked in chapter two: just because something is possible does not necessarily make it the right thing to do.

Since biopolitics is inherently always changing based on new technologies that redefine the boundary between nature and man, it is entirely feasible that the ethical foundations which inform biopolitics can shift. For this to occur, however, the applications of this technology must become normalized; serving as the means to shift current regulations in gene therapy cited in chapter two. All that is needed for this to occur is tied to the concept of normalization which serves as a means for change while naturally being pushed forward with a driving force (i.e. the will)[14].

[14] The concept of normalization occurs in two forms in sociological theory. For the purposes of this thesis, normalization refers to "normalization process theory" which is a framework for understanding the social processes by which innovations such as technology become routinely incorporated in everyday work (May, C., et al., 2008). This is not to be confused with Foucault's use of normalization which appears his book *Discipline and Punish* as in this case normalization happens within the individual as an idealized norm of conduct.

The will to normalize the use of CRISPR-Cas9 in gene therapy is best explained by using Michael Foucault's concept of biopower. In his book, *The History of Sexuality: An Introduction"* he describes biopower as "an explosion of numerous and diverse techniques for achieving the subjugations of bodies and the control of populations" (Foucault, 1976, p. 140). Simply stated, bio-power is the control over each individual's body, which, when combined, come together to create the people's body. Through this, the people's body behaves as a unanimous force rather than many different actors behaving in their best interest.

Foucault advances on his assertion that bio-power and the state are intertwined as he mentions that the well-being of the people relates to governmental concerns of fostering the life of the population through *anatomo-politics* of the human body. It does so through regulatory controls of the body (such as birth, death and healthcare) through biopolitics of the population (Foucault, 1976, p.139).

While one might believe that fostering life is a basic human right and thus the state doesn't play a part in the bio-power dynamic, it is only a right because it is within the interest of the state (Arendt, 1973). This is because being able to maintain a healthy population is an integral feature and essential to the workings of the modern state and capitalism. Hence, it can be understood that the regulatory frameworks regarding the body are set by the state are with the sole intent of to "make live and let die" (Foucault, 1976, pp.136-161) and are therefore an exercise of power in the service of maximizing life.

It is precisely this state incentive to grow in power by having healthier subjects that makes a strong argument for its motivation to pursue the use of CRISPR-Cas9 in humans via gene therapy. After all, CRISPR-Cas9 can not only edit the human genome, but it is doing it with increasing precision and cost effectiveness which put it at a distinct advantage over other gene

editing technologies like ZFN (expensive) and TALENS (inefficient). When this trait is combined with CRISPR-Cas9's potential to cure many genetic and some nongenetic illnesses (i.e. retroviral diseases), it could not only save lives, but also extend the lives of many people and increase their quality of life. This in turn would make the state more powerful by harnessing a larger, healthier, and longer lasting workforce that can increase its productivity.

While any significant use of CRISPR-Cas9 remains to be seen on humans, the driving forces for it are very real which give credence to the theoretical framework I established above. One example of this is the current competition between the United States and China. These two countries have invested the most in CRISPR-Cas9 research as getting gene edited cells into clinics across the world gives them more power over the other. Since CRISPR-Cas9 was developed as a gene editing technology, both countries have made substantial progress. However, this rivalry escalated in 2016, China was the first to test CRISPR-Cas9 on humans and sparked talks about "biomedical duel" on the progress of CRISPR-Cas9 gene editing (Cyranowski, 2016). Since then, both countries have continued to outline protocols for new gene therapies involving humans (such as new treatments for leukemia and other forms of cancer) at a rapid pace, suggesting that there is, in fact, a force pushing this research.

It is important that I emphasize that biopower need not be purely driven by the state. Rather, the state can use its sovereign power (i.e. through regulations and/or funding) as a driving force in favor of CRISPR-Cas9 in the biotech industry. This, in turn, can increase the state's biopower since the products of the biotech industry are subject to its regulation. This relationship is outlined in *The Rise of the Ethical License* which asserts that patents can be used

to manipulate the applications of technologies like CRISPR-Cas9 (Guerrini, 2017)[15]. In other words, government patents/ licensing can stimulate the market by incentivizing CRISR-Cas9 research through the possibility of future profit and as such the government can use the biotech industry to gain further biopower.

The stimulation of the market for CRISPR-Cas9 has resulted in its commercial proliferation such an incredible rate that *Scientific American* has called it "a genetic gold rush". This is certainly not a hyperbole as pushes by the biotech industry to use CRISPR-Cas9 is leading to deals worth (in some cases) billions of dollars (Megget, 2016). To highlight how highly CRISPR-Cas9 is being sought after for its potential monetary benefit, a patent debate at the very heart of the CRISPR-Cas9 community is under way over who owns the technology as intellectual property (Starling, 2017)[16].

Further, this competition both between institutions, the industry, and the state suggests that CRISPR-Cas9 is serving as a driving force because of the great financial opportunity it presents as well as the greater potential to increase biopower. It is this driving force that lends the potential to accelerate the progression of CRISPR-Cas9 research and its subsequent implementation on humans. However, returning to the fact that this technology deals with life itself, the driving forces advocating for the use of CRISPR-Cas9 in gene therapy are limited by restrictions predominantly related to its ethical use.

[15] While in this article the authors specifically argue that issuing patents can be used to restrict controversial applications, any state decision regarding restrictions is a form of control and hence why the biotech industry serves as a means for state biopower.

[16] The ongoing patent debate is between UC Berkeley and the Harvard Broad Institute in the case: *The Broad Institute, Inc. v. The Regents of the Univ. of California*. Declaration of Interference No. 106,048 (2016). On February 15, 2017, patent judges ruled in favor of The Broad Institute saying that the patent claims did not interfere with each other. This decision, however, has since been appealed by UC Berkeley through the U.S. Court of Appeals for the Federal Circuit. Hence, the patent debate remains open.

Throughout contemporary society, the normalization of using CRISPR-Cas9 in humans is already occurring, setting the stage for its use in gene therapy, and, following this trajectory, transcending current regulations. This process is loosely modelled after Georgio Agamben's notion of bare life and the role it plays in normalizing biopolitical technologies (such as CRISPR-Cas9). While developing the notion of bare life, Agamben derives the distinction between the mere biological existence (Zoë) and the ethical being through political life (Bios) from both Aristotle and Hannah Arendt. Agamben then builds on this when he introduces his own interpretation in *Homo sacer: sovereign power and bare life* where he draws on the Roman figure of law to question the nature of law and power. He does this by posing the Homo sacer, who is manifested by an expelled man who can be killed with impunity but is unworthy of either juridical punishment or religious sacrifice. Thus, the Homo Sacer is merely a figure exposed to murderous violence that also has no political significance which Agamben poses as a representation of bare life (Agamben & Heller-Roazen, 1998. pp.12-44).

Agamben applies this concept in his essay, *No to Biopolitical Tattooing*, where he exemplifies that anyone coming to America must get their fingerprints on file, as they are bare life since they are not American citizens by law. This process then becomes more normalized as more and more immigrants are fingerprinted to the point where the process of recording finger prints becomes more bio-politically acceptable to the point where people can use finger printing voluntarily to unlock their phone.

However, modernity has led to the implementation of other means of exploiting the Zoë and therefore expanding it to a new threshold and "could well be the precursor to what we will be asked to accept later as the normal… in the gears and mechanisms of the state" (Agamben & Murray, 2008 p.202). This allows the sovereign to legally control the Bios through the Zoë by

attempting to normalize borderline concepts. Once this normalization occurs, the restrictions previously held together by politics centered around ethics can be reduced by becoming more bio-politically acceptable. This is where the link between CRISPR-Cas9 use on humans and Agamben's notion of bare life come full circle as modern biopolitical technologies are being normalized through the implementation on humans with varying levels of Bios (or Zoë depending on how one looks at it).

In humans, the simplest level of bare body comes from the most basic unit of life: the cell, or rather the somatic cell for clarification. After all, assuming consent has been granted by the owner, the cell does not possess any level of political will. Rather, any political/ ethical implication on cell research is granted by the people who own the cell line. Because of this absolute absence of political will, naturally, the first application of CRISPR-Cas9 in human genome editing was on the human somatic cell line 293FT, which was used to suggest that CRISPR-Cas9 can be used to edit eukaryotic mammalian cells (Cong, L. et al., 2013). According to the authors, while the accuracy and efficiency of CRISPR-Cas9 was not perfect, improvements can be made regarding different Cas9 enzymes and PAM requirements. With this, the stage was set for further use.

The scientific community greeted this paper with open arms and soon after CRISPR-Cas9 gene editing was integrated to target diseases in mice, serving as a precursor to gene therapy in humans. This progress is perhaps best epitomized by the December 2013 study that successfully cured mouse cataracts by editing the *Crygc* gene (Wu, Y., et al., 2013). While admittedly the early use of this technique was not exclusive to human cells, the same principal applies due to the lack of bios lab mice possess.

Furthermore, the general acceptance of this application on human cells and other species lacking bios served to normalize this early potential for CRISPR-Cas9 use in gene therapy. Through said normalization researchers were able to continue to develop this paradigm by further pushing studies into areas of added relevance to gene therapy. For example, in an August 2014 study, the HIV-1 was successfully removed gene from the human genome by using human cell lines and the researchers referenced its potential future applications of this research explicitly as a form of gene therapy (Hu, W., et al., 2014).

While the use of CRISPR-Cas9 on human somatic cells was easily normalized and ethically justified based on its exclusive use on the Zoe, its application as a gene therapy eventually must infringe on the bios to serve as an instrument of biopower. In April of 2015, this breach occurred when researchers from Sun Yat-sen University used CRISPR-Cas9 to modify the gene responsible for β-thalassemia, a potentially fatal blood disorder (Liang, Puping, et al, 2015). While the results were largely unsuccessful, their choice to use non-viable human embryos led to controversy as scientists and researchers argued that it violated ethical concerns. While, these concerns were mainly related to the potential for germline edits (Cyranowski & Reardon, 2015), their off-target mutations are largely to blame because this was not a" safe" procedure.

Clearly the reaction from the use of non-viable embryos versus cells is indicative that the process infringed upon what some consider to be ethical. This is a product of the embryo, regardless of whether it is non-viable, having more bios than a cell. After all, the bios is assigned by the sovereign and the fact that a human embryo more closely resembles a human than a cell or another species has historically given it more agency. Furthermore, because of this experiment, a conference held at the National Academy of Sciences in December of that year was much like

that of Asilomar and Inuyama in that it called to establish ethical regulations, this time governing CRISPR-Cas9 research on humans. Similarly, it also appears that this conference was inevitable as the advent of CRISPR technology once again infringed upon our place in nature, the study on non-viable embryos was the mere catalyst.

Much like Inuyama, the 2015 conference aptly named the International Summit on Human Gene Editing ruled in favor of many regulations paralleling those of Inuyama, most importantly that the use of germline editing was irresponsible given the safety concerns. (Travis, 2015). Ironically enough, around the time the summit was held, the wrench in the equation was preparing to be thrown only a few hundred miles north of Washington D.C.

In early December 2015, Feng Zhang re-engineered the Cas9 enzyme into the *S. pyogenes* Cas9 enzyme (eSpCas9) with dramatic results as "off-target editing" was reduced to undetectable levels in the specific cases examined (Slaymaker, I., et al., 2016). Because of the enhanced accuracy of the eSpCas9 enzyme, the safety issues that were the essence of the International Summit on Human Gene Editing were largely undermined. This has opened the door for many more potential uses of gene therapy.

However, the technology has not been fully normalized yet even despite the added safety. This largely has played a role in the decision to approve human trials using this modified CRISPR-Cas9 on patients with leukemia. The experiment, unfortunately, is merely a trial to assess the safety of these techniques on humans (Reardon, 2016). By using terminally ill patients, the framework for normalizing this technology is further suggested, since it is a step forward from working on the pure Zoë of cells, but the patients still lack a full political will since they have few choices besides this treatment.

If the studies planned for 2017 and beyond are successful, then this pattern of normalization could soon continue to those that have increasing political will. The next step would likely be to use CRISPR to cure genetic forms of blindness, namely *retinis pigmentosa* (Suzuki, K., et al., 2016). Here, again the same pattern of increasing infringement upon the bios can be observed, as one has increasing agency to decide whether they want they to partake in gene therapy.

If this pattern continues, then it is entirely possible that CRISPR-Cas9 can become so normalized in society that it becomes part of our everyday lives, much like Agamben's example with finger printing. Doing so, would require a massive shift in regulation, nevertheless. Assuming Lemke is correct that the regulation of biotechnology is the product of politics based on bioethics (Lemke, 2011, p.26), the increasing ability of CRISPR-Cas9 to both respond to ethical concerns as well as shift the boundary between man and nature clearly give it the potential to undermine current gene therapy regulation. When this is coupled with a strong drive from biopower as well as the means to be normalized, this potential can be fulfilled. With this in mind, it is of the essence to plan for the possibility of a shift in bioethics which will be elaborated on in the next chapter.

Chapter Four:

How CRISPR-Cas9 can shift the ethics of gene therapy

In previous chapters, I suggested the mechanisms that give CRISPR-Cas9 the potential to shift the ethics of gene therapy. In this chapter, I will combine and elaborate more on what I established in previous chapters to suggest that CRISPR-Cas9 gene editing may serve as a catalyst to shift regulations in gene therapy. To do so, I want to first summarize key points from previous chapters to serve as context:

Chapter one established the relationship between CRISPR-Cas9 and gene therapy. In this chapter, I talked about what CRISPR-Cas9 is from a technological standpoint and used this knowledge to better explain trends in its increasing efficacy to edit genes and its decreasing cost. In addition to this, I also postulated that these trends would ultimately lead to new ethical issues as a new era of molecular biology begins.

Chapter two established that the Declaration of Inuyama set forward regulations on gene therapy that were largely informed from utilitarian, Kantian, and liberal ethical frameworks. Said frameworks established that gene therapy should be limited to somatic cells and should not be used for enhancement purposes. Further, these decisions were largely framed on notions that the technology driving gene therapy was both unsafe and very expensive.

Chapter three established the biopolitical drivers of CRISPR-Cas9 research through the concept of biopower as well how this technology can become normalized in society. I named these interacting forces the will and the means because they complement each other to push this technology across into society.

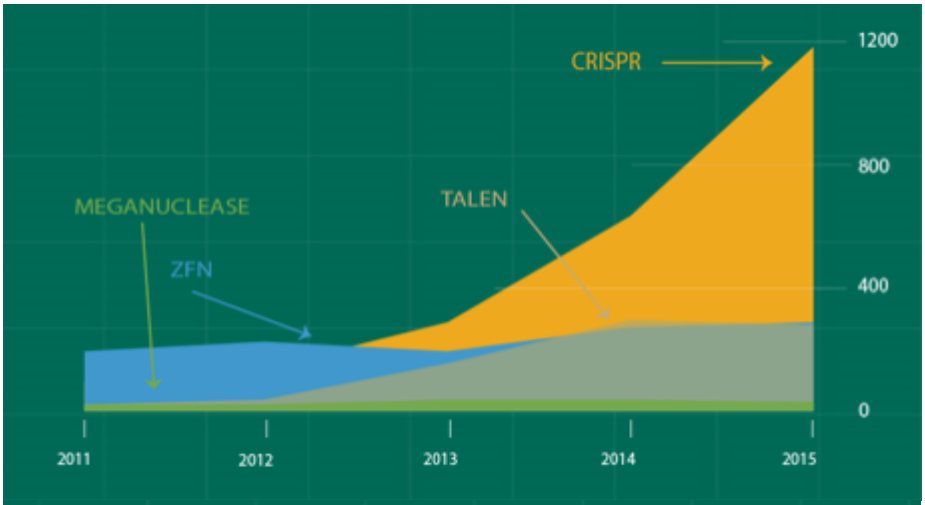
From the material I have provided above, it is evident that the ethical notions set forth by Inuyama are becoming increasingly obsolete with the advent of CRISPR-Cas9 gene editing technology via advances in both its accuracy and efficiency. Furthermore, when these aging ethics are met with biopolitical forces advocating for the increased use of gene editing on the human bios, the table is set for their shift. At the very heart of these developments is the disruption that CRISPR-Cas9 is causing in gene therapy. Because this disruption is so central to the issue, it is where I will begin my discussion of how this shift will occur.

Before I begin to elaborate, first, I want to underscore that the regulations behind gene therapy are informed by its ethics. Because of this relationship, a shift in ethics will almost certainly result in a shift in its regulation. Hence, it could have a substantial impact not only on gene therapy, but on society. I will discuss more on this issue at the end of the chapter.

CRISPR-Cas9 as a disruptor to gene therapy

When gene therapy first began, it was limited to the delivery of nucleic acid polymers into a patient's cells. In turn, said polymers would be expressed as proteins or interfere with their expression (Ermak, G., 2015). This meant that gene therapy was very limited because it could only influence very specific disorders, oftentimes with little success. However, as I explained earlier with Kuhn's "puzzle solving" framework, gene editing was already a part of the puzzle. Therefore, it is of no surprise that eventually the technology developed to allow this to occur (i.e. ZFN and TALENS). While these technologies did have moderate success, when *most* people think of gene editing, it is CRISPR-Cas9 that dominates conversation, even though both ZFN and TALENs have already shown moderate success in gene therapy. This is opposed to CRISPR-Cas9, which is only now (as of February 2017) beginning human trials.

When I say this, I am not speaking anecdotally. In the past few years the number of publications with relation to CRISPR-Cas9 and gene editing has greatly surpassed those of both ZFN and TALEN as is evidenced in the following figures.[17]



Name	Scholarly Output (2011 - 2015)	Avg. Citations per paper	Avg. Citations per paper with corporate collaboration
CRISPR	2,339	26.5	95.3
Meganuclease	132	16.9	2.7
TALEN	783	23.6	30.6
ZFN	1,180	11.1	26

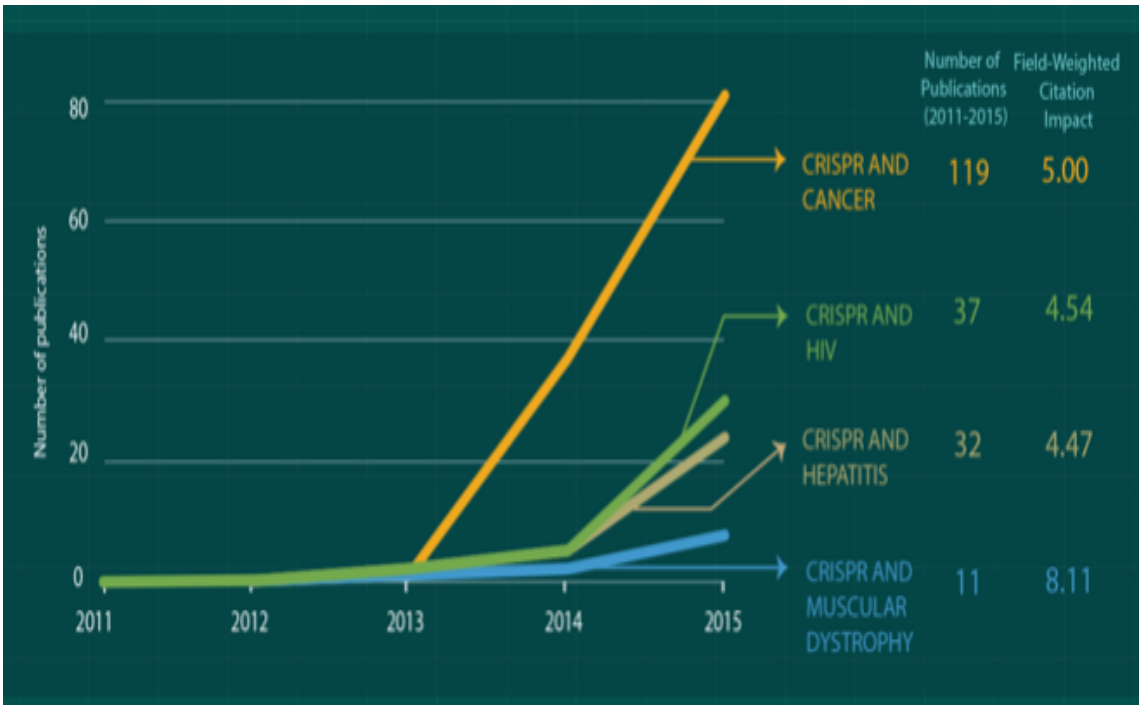
It is evident from these figures that CRISPR research is currently dominating the field of gene editing. What's more revealing is the almost quadratic shape of the curve for CRISPR which indicates an exponential growth in said research. This suggests that there is a lot of

[17] Both figures are published by Elsevier with data obtained through December 10, 2016 from SciVal https://www.elsevier.com/research-intelligence/campaigns/crispr

excitement about CRISPR within the gene editing community simply based on how fast research on CRISPR is growing. Clearly, the excitement behind CRISPR-Cas9 within the scientific community indicated that that there is something special to it. After all, to the outside observer, the fact that the largely unproven CRISPR-Cas9 is dominating its respective research field seems counter intuitive. So, what makes CRISPR-Cas9 so special?

As was discussed in chapter one, CRISPR-Cas9 is becoming increasingly cheap and effective when compared to previous technologies. Given this, CRISPR-Cas9 has the potential to overtake these more established technologies to become the king of gene therapy simply because of its economic value. Furthermore, since CRISPR-Cas9 is cheaper to use, it can be applied more broadly in gene therapy, which, when combined with its increasing accuracy, the quality of its edits should not be sacrificed.

It is through this potential that CRISPR-Cas9 is creating a disruption in gene therapy because the attention that has resulted from the opportunities it presents as both a cheaper and safer means of gene editing is changing the landscape of biomedical research. For example, companies like Novartis, Johnson & Johnson and many other startups are beginning to use CRISPR-Cas9 to create new immunotherapies (Ally, 2016). The following graph illustrates the extent of which CRISPR-Cas9 is disrupting gene therapy, because assuming there are limits to funding, an increase in the amount of CRISPR publications is resulting in decrease of other similar areas of research.



From this graph[18], it is evident that CRISPR-Cas9 is influencing the amount of research going into gene therapy. What is subtler, however, is that this is all done through gene editing as opposed to what is more considered more "traditional" gene therapy (i.e. delivering nucleic acid polymers). This only heightens the implications of a CRISPR-Cas9 disruption to gene therapy by revitalizing the field in unprecedented ways. Because of this "renaissance" of gene therapy, talks about its regulation are becoming more prevalent.

This is where the Declaration of Inuyama becomes key because as mentioned in the last chapter, the first meeting to talk about regulating CRISPR-Cas9 in December 2015 essentially reaffirmed the regulations established by the Declaration of Inuyama. However, because CRISPR-Cas9 is disrupting gene therapy through tremendous increases in research, the technological advancements it is yielding are on pace to make the current restrictions in place obsolete.

[18] CRISPR info graphic published by Elsevier with data obtained through December 10, 2016 with data from SciVal https://www.elsevier.com/research-intelligence/campaigns/crispr

Revisiting the Declaration of Inuyama

What I mean by saying "obsolete" is that the premises by which the restrictions were developed no longer apply. Once this occurs, then new restrictions must be put in place to maintain order. This is where the biopolitical forces I talked about previously come into effect. Because there is both a will and a means to normalize CRISPR-Cas9 gene editing, there is a driving force advocating for the continued infringement upon the bios. Left unchecked, these forces can be very dangerous as they can lead to but not limited to enhancement, eugenics, and creating greater disparities between people/countries. The trick is to balance the restrictions to allow for more favorable outcomes while not suppressing the positive impact new developments to gene therapy can have.

To create this balance, we should look no further than Declaration of Inuyama. Even though times have changed and more recent conferences have taken place, the fact that these conferences essentially reaffirm the basic principles of Inuyama suggest that the prioritization of liberal, Kantian, and utilitarian ethical frameworks is still relevant. Hence, by looking at said priorities, it is possible to see how these frameworks can shift to continue being accepted while remaining appropriate to the technological advancements made possible by CRISPR-Cas9.

Liberal Ethics: Enhancement

Liberal (Rawlsian) ethics were emphasized in the Declaration of Inuyama by maintaining that gene therapy could only be used to treat genetic illness and could not be used for enhancement purposes. While admittedly there are a lot of many nuanced issues at hand with

enhancement, one of the main backbones for this regulation has to do with the social impact enhancement it could cause. This is because genetically manipulating anything other than an illness could lead to greater disparities in populations. If an individual could select specific traits, this could give them a competitive advantage over others in many regards such as physique, intelligence, or even lifespan (through telomere extensions). Furthermore, while this thinking was already in place in the Declaration of Inuyama (refer to chapter two), the capabilities simply did not exist and thus this regulation seemed more as a precaution. This is no longer the case as CRISPR-Cas9 gene editing has successfully manipulated 62 genes at once. (Yang, et al., 2015) This currently places CRISPR in the range of being able to edit traits such as eye color which requires 16 genes (White & Rabago- Smith, 2010) and doesn't this doesn't even account for future innovations resulting in more genes being edited at once.

Enhancement would certainly result in a disadvantage to those who abstain from gene editing for a variety of different reasons. What's now different from when the Declaration of Inuyama was written is that if CRISPR-Cas9 makes enhancement affordable, there are still reasons people could choose not to undergo enhancement. Therefore, allowing for enhancement could detract from personal freedoms such religion, access, cultural and beliefs due to the competitive nature of society by forcing people to adapt to this competition. Thus, even if enhancement becomes affordable, it still violates the liberal principal of equality because people are not equally able to make these decisions. Therefore, if a shift in ethics were to occur, the restrictions on enhancement will likely remain in place based on ethical precedents.

What *can* change because of this increased affordability, however, is the scope of which gene therapy can be used. This is because work with CRISPR-cas9 has led to considerable progress in researching treatment options in non-genetic disorders such as HIV (Hu, W., et al.,

2014) and organ donation (Yang, et al., 2015). If alternate uses for gene therapy such as this are made available, then new regulation would be likely be needed for a more interdisciplinary approach to treat such illness. This is because treatment for these disorders extends beyond just the genetic approach and requires more multifaceted interventions (i.e. social, surgical... etc.) which would require further regulation given new opportunities through gene therapy.

Kantian and Utilitarian Ethics: Germline Manipulation

The ban on germline manipulation by the Declaration of Inuyama is more complex in ethical terms. On one side, the use of germline manipulation could spell the end for many terrible genetic diseases such as X-linked SCID, chronic lymphocytic leukemia, and Parkinson's disease. On the other is the potential devastation that could be inherited for generations if something goes wrong. The latter reasoning is why there is a ban on germline manipulation and is founded on Kantian ethics due to the moral obligation to treat all humans as an end.

Moreover, Section VI of the Declaration of Inuyama[19] makes it possible to continue ethical discussions on this issue. Thus, Kantian ethics also lays out the possibility for a shift in germline regulation to occur. As was discussed in chapter two, the safety of making such corrections is a major barrier. However, if the technology becomes safe, then human germline editing suddenly become an end. In this case, Kantian ethics would make it morally flawed not to allow patients undergo such a procedure due to the negative health effects a genetic malfunction has on them and future generations.

[19] See Appendix A

The development of the eSpCas9 enzyme which has made CRISPR-Cas9 much more accurate, in addition to the possibility of increasing this accuracy overtime may eventually resolve this issue by making germline editing safe. This safety is complemented by an increased understanding of the genetic basis of disease. Interestingly, CRISPR-Cas9 is getting to a point where it can become limited by the amount of genomic information available and thus both gene editing and genomics will need to work together to increase the safety of germline manipulation. With this combination, it can eventually be possible to treat germline editing as an end which per Kantian ethics should result in its adoption into the gene editing paradigm.

Evidence of this is already beginning to occur. In 2015, the UK ruled for the NHS backing of tri-parental embryos. While not technically editing a gene per se, this procedure introduces the DNA of both parents into a donor egg with healthy mitochondrial RNA (mRNA). In doing so, a potential cure for mitochondrial diseases is in place by replacing defective mRNA (Mitalipov, S., & Wolf, D., 2014). This sets up an important precedent for the use of germline gene editing since the technique is already being used and helping improve quality of life. More importantly, however, on Valentine's day of 2017, the National Academies of Sciences, Engineering, and Medicine recommended that germ-line modification be permitted in the future[20]. This, however, does not allow for germline modification just yet. Rather it acknowledges that there is a potential in certain narrow circumstances to prevent the birth of children with serious diseases using this technology.

These events suggest that if CRISPR-Cas9 can work effectively and safely, then it could become more "morally correct" to use these techniques to save lives. Thus, the Kantian

[20] The report is available online at the National Academies of Science, Engineering and Medicine website and is free to download (https://www.nap.edu/download/24623)

framework of germline regulation may certainly shift regulations to afford the possibility of future germline modification.

Furthermore, it is not enough to suggest that the increased safety of germline modification is enough to solely drive this shift. After all, if there are more viable alternatives such as IVF and genetic screening to germline manipulation, then the cost of using it is greater than its benefit. While there is no clear-cut answer to which technique has more utility, with a CRISPR-Cas9 disruption, the utility of alternate techniques could be reduced. This is a result of both a reduction in price and the fact that germline manipulation would reduce the need for their use by stopping genetic illness at its source.

Additionally, the utilitarian ethical framework laid out in the Declaration of Inuyama suggested a ban on germline manipulation research. However, because CRISPR-Cas9 did not develop solely for germline manipulation and it is rather a byproduct of its ability to edit genes, its use bypasses this principle once the technology becomes more accurate through other avenues of research. Hence, the benefits may override the costs of developing germline manipulation techniques with CRISPR-Cas9. Once again, this would lead to a shift in ethical priorities because it is becoming more efficient to invest these resources in germline manipulation since it gets to the route of the problem as opposed to using resources on a case by case basis.

Why we should care?

The ethical issues regarding gene therapy are undeniably complex. They require finding the right balance between what is a cost to society versus its potential benefits due to the subjectivity of prioritizing different ethical frameworks. Whereas currently these issues pertain primarily to germline gene editing as well as the limits to the medicinal application of gene editing, the disruption caused by CRISPR-Cas9 in gene therapy can cause regulations to change. Change can be scary. Yet, by focusing on how gene therapy can change from an ethical perspective, it has become apparent that this change should not be scary and can even be exciting.

After all, an ethical shift is not inherently good nor bad, since ethics are simply established societal standards. Therefore, any change represents what society finds suitable. That being said, such changes allow for a more appropriate response given our increased knowledge and capabilities made possible by CRISPR-Cas9. Additionally, because biopower serves as a constant force pushing for the increased use of CRISPR-Cas9 in the bios of humans, there is a likelihood that this push can again further shift ethics of gene therapy. This push is what fuels the *Gattac*a-like dystopian scenarios such as designer babies or species-specific bioweapons.

Nevertheless, even if CRISPR-Cas9 is eventually able to fulfill our gene editing dreams, ultimately we are the ones in charge. We are the ones who have the privilege to decide how gene editing technologies can shape our future. Therefore, there is a particular weight placed on those who create these regulations, making it imperative that they represent the best interests of society.

Appendix A

THE DECLARATION OF INUYAMA

Human Genome Mapping, Genetic Screening and Gene Therapy

I. Discussion of human genetics is dominated today by the efforts now under way on an international basis to map and sequence the human genome. Such attention is warranted by the scale of the undertaking and its expected contribution to knowledge about human biology and disease. At the same time, the nature of the undertaking, concerned as it is with the basic elements of life, and the potential for abuse of the new knowledge which the project will generate, are giving rise to anxiety. The Conference agrees that efforts to map the human genome present no inherent ethical problems but are eminently worthwhile, especially as the knowledge revealed will be universally applicable to benefit human health. In terms of ethics and human values, what must be assured are that the manner in which gene mapping efforts are implemented adheres to ethical standards of research and that the knowledge gained will be used appropriately, particularly in genetic screening and gene therapy.

II. Public concern about the growth of genetic knowledge stems in part from the misconception that while the knowledge reveals an essential aspect of humanness it also diminishes human beings by reducing them to mere base pairs of deoxyribonucleic acid (DNA). This misconception can be corrected by education of the public and open discussion, which should reassure the public that plans for the medical use of genetic findings and techniques will be made openly and responsibly.

III. Some types of genetic testing or treatment not yet in prospect could raise novel issues - for example, whether limits should be placed on DNA alterations in human germ cells, because such changes would affect future generations, whose consent cannot be obtained and whose best interests would be difficult to calculate. The Conference concludes, however, that for the most part present genetic research and services do not raise unique or even novel issues, although their connection to private matters such as reproduction and personal health and life prospects, and the rapidity of advances in genetic knowledge and technology, accentuate the need for ethical sensitivity in policy-making.

IV. It is primarily in regard to genetic testing that the human genome project gives rise to concern about ethics and human values. The identification, cloning and sequencing of new genes without first needing to know their protein products greatly expand the possible scope for screening and diagnostic tests. The central

objective of genetic screening and diagnosis should always be to safeguard the welfare of the person tested: test results must always be protected against unconsented disclosure, confidentiality must be ensured at all costs, and adequate counselling must be provided. Physicians and others who counsel should endeavour to ensure that all those concerned understand the difference between being the carrier of a defective gene and having the corresponding genetic disease. In autosomal recessive conditions, the health of carriers (heterozygotes) is usually not affected by their having a single copy of the disease gene; in dominant disorders, what is of concern is the manifestation of the disease, not the mere presence of the defective gene, especially when years may elapse between the results of a genetic test and the manifestation of the disease.

V. The genome project will produce knowledge of relevance to human gene therapy, which will very soon be clinically applicable to a few rare but very burdensome recessive disorders. Alterations in somatic cells, which will affect only the DNA of the treated individual, should be evaluated like other innovative therapies. Particular attention by independent ethical review committees is necessary, especially when gene therapy involves children, as it will for many of the disorders in question. Interventions should be limited to conditions that cause significant disability and not employed merely to enhance or suppress cosmetic, behavioural or cognitive characteristics unrelated to any recognized human disease.

VI. The modification of human germ cells for therapeutic or preventive purposes would be technically much more difficult than that of somatic cells and is not at present in prospect. Such therapy might, however, be the only means of treating certain conditions, so continued discussion of both its technical and its ethical aspects is essential. Before germ-line therapy is undertaken, its safety must be very well established, for changes in germ cells would affect the descendants of patients.

VII. Genetic researchers and therapists have a strong responsibility to ensure that the techniques they develop are used ethically. By insisting on truly voluntary programmes designed to benefit directly those involved, they can ensure that no precedents are set for eugenic programmes or other misuse of the techniques by the State or by private parties. One means of ensuring the setting and observance of ethical standards is continuous multidisciplinary and transcultural dialogue.

VIII. The needs of developing countries should receive special attention, to ensure that they obtain their due share of the benefits that ensue from the human genome project. In particular, methods and techniques of testing and therapy that are affordable and easily accessible to the populations of such countries should be developed and disseminated whenever possible.

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