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Designer Babies: A Paired Analysis of the Technological Advances and Ethical Implications of Genetic Selection

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An Introduction

Imagine this. A baby with flawlessly sculpted facial features, perfectly curled toes, cooing without a hint of present or future debilitating conditions. What could possibly be awry with this seemingly picture-perfect creation? The answer, as one may suspect from this pointed question, is more multifaceted than it may initially seem.

In a society where its popularity continues to trend upward, the practice of trait selection has lead to the coining of a phrase that has successfully commanded the attention of both the science and non-science communities alike. *Designer babies*; a feat possible due to rapid technological advancement in recent years. While the development of such novel advancements is always expected to generate a variety of misconceptions, the widespread belief of one, in particular, arguably has the potential to transform society before our eyes. The notion that 'designer babies' are a phenomenon of the distant future, if at all, is the alarming naivety that will permit this technology's transformative powers. The technology to genetically engineer is here and has already been utilized for the genome alteration of numerous organisms. The insatiety of human nature, with respect to technological advancement, provides reason to believe that, given the foundation of successful creation of 'designer' plants and animals, the anticipated creation of 'designer humans' is almost guaranteed.

The creation of 'designer babies' would remain simply a figment of genetic researchers' imaginations if it were not for the technological advancements of the twentieth century. Presently, four methods of genome editing exist: Zinc Finger Nucleases (ZFN), Transcription Activator-Like Effector Nucleases (TALEN), Clustered Regularly-Interspersed Short Palindromic Repeats (CRISPR), and Multiplex Automated Genomic Engineering (MAGE). Each exhibits slight variations from the next, yet the underlying notion of the general mechanism

is consistent. Genome editing techniques share their reliance on a particular enzyme to identify a specific region of DNA, bind to it, create a double-strand break (DSB) in the DNA, and repair the genetic breach. It is the specific, low-level variations in this general mechanism, however, that account for technique differentiation. For reasons to be elaborated upon following additional background, the present composition will primarily devote its attention to the CRISPR technique.

While this technological advancement for genetic engineering may seem to provide long-awaited answers, it is vital to recognize that it poses many newfangled questions, as well. Acknowledgement of, and reflection on, these untrodden ideas is critical, as their answers represent what we will permit as a society. These decisions ultimately fall into the hands of the parents who intend to create designer babies. It would be a grave mistake, however, to underestimate the role of society in dictating the future of this advancement. The allowance, degree of allowance, or prohibition of genetic engineering will significantly affect dynamics in the workplace and schools, healthcare and legal systems, and insurance rates, among many other possibilities. It quickly becomes evident that the choices of individual parents will inevitably exert at least some degree of influence on those not using the technology, quite possibly against their will.

The combination of this vast sphere of influence and the boundless nature of ethical ramifications renders it nearly impossible to address every ethical dimension of genetic engineering. Thus, in hopes of enhancing the imperforate nature of this analysis, I have chosen to narrow the subsequent rationale to a highly-integral dimension, *the parental choice*. This is certainly not to say that we can ignore society's role from this point forward; in fact, this is far from the truth. These parents *are* part of society. Each ultimately reflects the other, existing in a

bidirectional relationship where one can never truly separate from the other. Parents are influenced by what society thinks is best or worst, and society is, in turn, affected by the parental reinforcement of what traits they value most and select for.

The development of genome editing technology inevitably comes with a variety of pressures applied by society. Thus, parents absorb this additional pressure to generate the perfect child. If the resources are available to do so, and other parents are utilizing the technology to create a perfect human, what disadvantages exist for a non-designer individual? Additionally, disadvantages can be realized in any life stage: as a baby, when competing for attention in daycare and subliminal human tendencies result in increased care for the more attractive designer baby; as a child, in an educational setting; and finally, as an adult in the workplace. Under this pressure, an ethical dilemma develops in that a parent's decision to utilize the technology may become less of a reflection on their ethical beliefs, and more on the coercion induced by societal pressure.

The thesis at hand seeks to evaluate not only the underlying scientific mechanisms that enable the prospect of genomic engineering, but also the ethical implications that inevitably arise alongside the technology. As I devised the initial stratagem for this composition, my intent was to give an precursory account of the science and technological advancements, followed by an analysis of the ethical implications that arise. It quickly became apparent, however, that these discourses are innately intertwined and, what is more, to perform analyses independent of one another would yield a product that greatly underestimates their connection. This underestimation gives rise to an issue of even greater concern; namely, the failure to convey that our response to the ethical implications of this rapidly developing technology have the power to dictate the future of this advancement. Upon great deliberation, I believe that the most effective delivery of this

comprehensive, yet focused, analysis of genetic engineering interlaces a high-level view of the societal implications with their low-level consequences for parents who choose genome editing.

The Cinematic Portrayal of Genetic Modification

While it may initially seem to be a non sequitur amidst the present scientific, technological and ethical content, the cinematic portrayal of genetic modification is far from irrelevant. Films that delve into the prospect of human engineering for the future illustrate the connections between art, science, philosophy, and ethics. These realms are, in essence, the elements united within this composition. While it is almost instinctual to disregard 'Sci-Fi' films as unrealistic and solely for entertainment, the analysis to follow offers the reasoning for a suggested alternative response.

Filmmakers indubitably include the unrealistic elements to pique the interest of their customers. However, even fictitious films such as *Blade Runner*, *Gattaca*, *Jurassic World*, *Blade Runner 2049*, and *Rampage* exist because humans fathomed their plots. Cinematic productions, regardless of their degree of realism, are the product of the human imagination; and, given the insatiate nature of human aspirations, what we imagine often becomes reality. Filmmakers possess an innate understanding of the human condition, an advantage that grants them the necessary insight to make their audience connect with aspects of even the most outlandish film. These elements of reality within fiction touch us, activating the fanatical, child-like dimension present in even the most mature human mind. *Could it really be true?* Often beneath the level of consciousness, they affect our thinking, our perspectives, and, ultimately, our behavior. It is the ingenious combination of thrill-inducing factors and 'just enough' reality to resonate with the human condition that accounts for this cryptic imprinting.

To align the present discussion more closely with the chief focus of this thesis, note the relationship that exists between the aforementioned persuasion and the establishment of ethical stances. In essence, a cinematic production is the compilation of opinions of those involved in its development. A novel-based film, for example, represents the incorporation of the author's original intent, the writer's adapted translation from novel to script, the film director's relay of the script, and the stars' interpretations of the director's instruction. Each influence adds a new spin that inherently influences the message conveyed by the final product. Thus, films serve as a popular mechanism for taking stances on contemporary issues and can, arguably, be likened to a 'philosophical laboratory.' Films that successfully connect with the human condition elicit a reaction, providing the desired feedback of such ethical 'laboratory tests.'

Thorough observation of the common threads among the films mentioned above promises a more compelling derivation of the crucial takeaways. *Blade Runner,* released in 1982, pairs the evil nature of human-resembling androids and human emotion to underscore the challenge of determining what it means to be human (IMDB. (n.d.)). In accordance with the science-fiction tendency to take place in the future, the 1982 film is set in the futuristic year, 2019. The hidden value in these fanciful, yet far from arbitrary, timelines exists in their ability to document attitudes and predictions. Thirty-six years after *Blade Runner*'s release, and with 2019 less than one year away, a valuable comparison of anticipation and reality can be made. While I do not foresee the rise of android villains occurring by next year, we have already witnessed the creation of robots who can both perceive and emote human emotion. Arguably the most apparent attitude conveyed is a forewarning unmistakably reminiscent of the *'Frankenstein'* dilemma. In both cases, the human fascination with devising another being "equal to himself" backfires. While it may be too late to heed this warning regarding emotional robots, the

impending prospect of designer babies will soon be reality, with continued pursuit of this forewarned fascination.

The 1997 film, *Gattaca*, explores the struggles of a man who is "genetically inferior," a condition that precludes him from "pursu[ing] his lifelong dream of space travel" (IMDB). Refusing to accept this fate as reality, he manages to "assume the identity of [his] superior" brother, a feat not without its own set of challenges (IMDB). One may liken the relationship and resulting emotions between a genetically superior and inferior sibling to the potential dynamics between designer and non-designer individuals of the future. The inevitable jealousy, qualification for particular occupations, and potential to divide society are among the numerous implications evidenced within the film.

Blade Runner's 2017 sequel, *Blade Runner 2049*, takes place in a society dictated by division between the human and artificial human populations. This distinction is disturbed by the creation of a new generation of artificial humans, or Replicants, who are bioengineered to have "implanted memories," "open-ended lifespans," and "modified behavior" for improved obedience (IMDB). These artificial humans are 'manufactured,' rather than 'born,' do not have souls and, initially, are devoid of the ability to reproduce. Humans possess little respect for Replicant life, particularly evident in the decision to 'retire,' or kill, a Replicant child without reservation, even after determining he had been 'born' and possessed a soul. This notion is confirmed, once again, in the unsettling human reaction to the prospect of engineering a Replicant species capable of reproduction. Their fear was not, as one might suspect, of a Replicant siege, but rather that they would no longer be able to "deny [the Replicants] their rights and freedoms" (IMDB). With respect to the prevalent concern that genetic engineering detracts from the dignity of the human person, this perfectly validates this exact notion.

The creation of a hybrid through genetic engineering, presented in the 2015 film, *Jurassic World,* bears striking resemblance to the designer baby phenomenon at hand. His curiosity beginning when he learns that the incorporation of frog DNA into the dinosaur genome enabled to switch gender, scientist Dr. Henry Wu is determined to perform a gene mixing to bring about a new species. He successfully created two hybrid plants, but he is not satiated by these achievements, eventually developing the 'designer baby' of the dinosaur realm. Fittingly named, *Indominus rex*, the monster is a genetic hybrid of numerous species including at least seven dinosaur species, along with "modern animals like cuttlefish, tree frogs, and a pit viper snake" ("Indominus rex". (n.d.).). "'Oh, Indominus wasn't bred,'" he flaunts. "'She was designed.'" ("Indominus rex"). This distinction is quite similar to the transition from genetic modification through artificial selection and genetic engineering, detailed in an upcoming section.

Based on a 1980's video game, the 2018 film, *Rampage,* presents an alternate view than the previously discussed films in that it specifically features CRISPR technology. The film's events stem from the infection of a beloved gorilla at the San Diego Zoo with a CRISPR mutagen from canisters were dropped from the international space station. The infection renders him dangerous to the human community. The apparent tension between the gorilla's devoted caretaker and the film's CRISPR scientist, who has a deceitful and criminal persona, draws attention to the concerning natures of the technology "inadvertently… weaponized by an evil, shadowy corporation," and the hazardous effect of this incident on the innocent animals ("Rampage: Behind-The-Scenes of the Dwayne Johnson Giant Monster Movie.", 2018). Though I could not yet find significant film commentary in order to support my suspicions, to be released April 13, it seems to fairly clearly present an ethical argument against the testing of CRISPR on innocent animals. As to be expected when complex biotechnology is adapted to fit the desires of

pop culture, certain truths become distorted and realities, misconstrued. Hyperboles abound, namely in CRISPR's use in the film "to splice dozens of animals together in the blood stream of host organisms" (Rampage). Film producer John Rickard's account of where CRISPR currently stands seems to convey a slight discrepancy in understanding that what has not been discovered yet is still being used as evidence that CRISPR is real. He states, "'everything that's happening in this movie is actually real. There's one piece of it that is science fiction that may become real in the next five to ten years that they're working on now. So, CRISPR is real.'" (Rampage) The film's prediction is characterized by its combination of CRISPR technology and an ability to develop a "delivery system" to quickly "spread [its effects] throughout the body." (Rampage) Such development is carried out by the villains of the film, an assignment that is likely far from inadvertent. (Rampage)

Ultimately, the varieties in the genetic engineering, predictions, and attitudes incorporated into each film can be reduced to a single notion: *a tireless quest for perfection.* Both the history of eugenics and the frequent cinematic portrayal of human phenotype alteration show an *obsession* with using genetic and reproductive technologies to control human evolution and direct it toward specific outcomes. In the current Netflix series, *Orphan Black*, for example, it is declared that the actions taken by a Biotech company are to create the perfect human genome for the first time in human history. However, the company's *original* motivation for pursuing this goal was *only* to cure and prevent a specific disease, gradually expanding to all disease, and eventually to create the 'perfect' human genome. Evidenced in ancient times, humans have demonstrated this proclivity to perform drastic, often unethical, measures to achieve what is considered 'perfect,' until it changes and we begin again. This obsession, thus, will not end until we feel we have created the perfect human genome; a task which is simply not

possible. Despite the natural human desire to achieve perfection, perhaps it is actually perfect to be *imperfect*. Each individual is so unique from the others that it, in reality, is our imperfections that make us 'perfect,' eliminating the possibility of any universal notion of perfection. Perhaps our flawed optimism and the elusive nature of our goal explain why humans can never contently discontinue our quest.

The inability of human beings to be satisfied with present conditions exemplifies the outrageous need for an address of the hugely consequential ethical implications. *If*, or maybe, based on this obsession, it is more realistically *when*, we perfect the concepts and techniques proposed in these cinematic laboratories, *then what*? This succinct query is all that is necessary to fully encapsulate the countless sought-after answers which consume the subsequent pages.

Introduction & History of Genome Editing

With all of the excitement surrounding the aforementioned advancements of the present era, it may be easily misunderstood that human use of genetic modification is far from new. Such modification originated in the domestication of various plants and animals through artificial selection and intentional breeding. Artificial selection, named based on the premise that humans choose which organisms will be bred, an 'artificial' act in comparison to nature's 'natural' selection mechanism ("Artificial Selection." (n.d.)). It follows that this intentional selection would mean breeding only those organisms with the desired characteristics. Intentional breeding operates under much the same premise as artificial selection ("Artificial Selection").

Genetic *engineering*, however, is slightly more novel. Taking the practice of genetic modification one step further, genetic engineering involves the deliberate manipulation of genetic material. Such modifications, achieved in a multitude of ways -- base pair alteration, deletion of DNA regions, or insertion of gene copies, even DNA from foreign organism -- allow

for the acquisition of desired characteristics, manifested in the form of a phenotype. ("What is genetic engineering?") Yet, the achievement of such sophisticated genome alterations was not without a series of revolutionary discoveries. An imperforate understanding of the nature and mechanisms of DNA laid the necessary foundation for the discoveries of the future. ("What is genetic engineering?")

A brief history of these crucial discoveries will prove beneficial in providing additional context for the advancements at hand. Dating back to the prehistoric era, artificial selection and breeding serve as the origin of genetic engineering for both plant and animal species. The nineteenth century's documentation of artificial selection and breeding, novel observations of genetic inheritance, the nucleus as the storage unit of genetic material, and the successful creation of an animal using in-vitro fertilization (IVF) allowed for a multitude of findings of the twentieth century. ("History of Genetic Engineering", n.d.) The years between the 1940s and 1960s proved essential in learning about the molecular basis of DNA, its role in genetics, and the link between mutations in genetic material and disease (BW). In particular, the 1950s were essential for attaining such knowledge regarding the nature of DNA (pres., source?), namely its double helix structure (1953) and semiconservative nature of replication (1958). Plasmids were discovered in 1952, enabling the cellular transfer of genetic information, as well as replication of DNA sequences (wiki). In addition to the proposal of DNA's double helix structure, 1953 also yielded the first human artificial insemination. (History of Genetic Engineering)

With the molecular basis of DNA known, the 1960s saw the "unraveling of the genetic code," as well as the genome manipulation with enzymes. The use of particular enzymes, known as DNA ligases, to anneal DNA fragments was successfully performed in 1967. Interestingly, the technique to reassemble fragmented DNA preceded the discovery of DNA splicing

technology. These splicing enzymes, capable of cutting DNA, were discovered one year later in 1968 and became known as endonucleases. (History of Genetic Engineering) Also in the 1960s, focused research on Sickle cell anemia, a condition resulting in deficient oxygen levels due to malformation of oxygen-transporting red blood cells, determined that the disease is caused by a single point mutation. ("Sickle cell anemia", 2018) A point mutation is characterized by the addition, deletion, or alteration of a single nucleotide base -- A, C, G, and T(DNA)/U(RNA) -- within a strand of genetic material. ("Point mutation", 2017) The specific order of bases determines the subsequent transcription of the mRNA strand, whose sequence codes for the particular amino acids that join together to construct specific proteins. A mutation in the foundational genetic material can, thus, result in the production of incorrect proteins. In the case of Sickle cell anemia, a base substitution mutation causes the production of the amino acid, valine, where glutamic acid typically resides. Two copies of this mutation results in sickle-shaped red blood cells, which cannot carry oxygen with the typical efficiency. (Point Mutation)

Restriction enzymes were discovered in 1970 by a team of researchers led by microbiologist, Hamilton Smith, which enabled researchers to cut DNA at specific sequences and separate them, and thus, isolate genes from the genome (wiki). Researchers soon determined that the combined use of restriction enzymes and DNA ligases enabled a 'cut-and-paste' function in DNA sequences. The product of this manipulation, which was fittingly named recombinant DNA, would prove to be a quintessential piece in the future of genetic engineering. By 1973, experimentation with recombinant DNA cloning took place. (History of Genetic Engineering) In addition to the genomic experimentations taking place, the 1970s witnessed a novel sort of advancement, one with particular relevance to the 'designer baby' phenomenon. In 1976, DNA was utilized to produce the first prenatal genetic diagnosis. Frederick Sanger and Walter

Gilbert's 1977 discovery of DNA's sequence of bases was arguably the most notable of the decade, as it increased the amount of genetic information available to researchers. Named after one of its pioneers, the DNA sequencing method became known as Sanger Sequencing. The end of the decade also yielded a significant number of genetic engineering advancements; namely, the 1978 birth of the first IVF test tube baby and the use of genetic engineering to create a method for insulin production. (History of Genetic Engineering)

The achievements of the 1980s can be characterized primarily as applications of the techniques discovered throughout the preceding decades: 1980s first mouse to be genetically-modified, 1984s birth of a human developed from a frozen embryo, the cloning of sheep embryonic cells in 1986, and the 1987 birth and development of transgenic mice containing human genes. The exception to this characterization certainly stands alone from the decade's other milestones. In 1983, Kary Mullis discovered a process called polymerase chain reaction (PCR). PCR is a technique used to amplify a small DNA segment into many copies of the specific segment, and is also beneficial for identifying and isolating genetic material. Arguably the greatest achievement of the end of the twentieth century was the complete mapping of the human genome, a feat named the Human Genome Project. Human application of gene therapy, a heart transplantation from a genetically modified pig possessing human genes to a baboon, and Dolly the sheep as the "first cloned animal." (History of Genetic Engineering) Though the twenty-first century may be in its early stages, the first human babies to be genetically modified were born in 2001 and the 2004 development of the first human clone in South Korea confirm the rapid progression of genetic engineering application.

It may come as a surprise that the knowledge allowing for the delineation above can largely be attributed to some of the planet's most primitive organisms, bacteria and archaea.

Many of the early studies that provided the foundation for contemporary progress were bacterial in origin. A fundamental experiment performed under the direction of Frederick Griffith in 1928 demonstrated the ability of particular bacteria to incorporate and express segments of DNA that were not their own. Morton Mandel and Akiko Higa's 1970 experiment confirmed this ability with the bacteria *Escherichia coli* (*E. coli)*. After treating the bacteria with a calcium chloride ($CaCl_2$) solution, a successful uptake of bacteriophage λ ensued, a phenomenon they called "artificial competence" (wiki). Stanley Cohen demonstrated these findings, once again, in 1972 in his use of the $CaCl_2$ treatment to produce the same phenomenon with plasmid DNA. The 1980s saw the introduction of electroporation, a technique used to pass a variety of molecules, including DNA, through the cell membrane, with the application of an electrical field. This introduction of "new coding DNA" enabled the alteration of bacteria, and increased efficiency and bacterial range, through a technique which came to be known as transformation. Following the 1907 and early 1970s discoveries of the bacterium responsible for plant tumors and a DNA plasmid as the tumor inducing agent, respectively, researchers witnessed a crucial ability of bacteria (wiki,24). When the tumor-causing plasmid genes were replaced by new genes, the plants infected with the bacterium were found to have transformed genomes containing selected portions of bacterial DNA (wiki,25). While genetic engineering would not be in its current stage without each discovery mentioned, the previous discussion omits the recognition of bacteria and archaea for one additional contribution, *CRISPR.*

The Mechanism of CRISPR

Long before it became pop culture's coined term for genetic engineering, CRISPR referred to a hidden gem only used by the other two biological domains. Bacteria and archaea, as rudimentary as they may be, have been using the technique, which humans are currently

struggling to perfect, as their immune system for billions of years. Discovered by Japanese scientists in 1987, a portion of their DNA is organized into "**c**lustered **r**egularly **i**nterspaced **s**hort **p**alindromic **r**epeats" (Sti1, n.d.). It is from this defense mechanism that the *CRISPR* of eukaryotic interest derives its name.

Research has revealed that the repeating genetic segments are separated by "short, non-repeating spacers" of foreign DNA (Sti1). The immunological properties lie within the contents of these spacers sequences. These spacer sequences are DNA copies of sequences from viruses previously encountered by the bacteria or archaea (Sti). Should the organism encounter this virus again in the future, this diary-keeping of the exact information necessary to target the invader the next time yields several advantages; namely, heightened recognition and faster attack (Stierwalt, S., n.d.). The immunological benefits of human vaccinations can be explained by the identical principles.

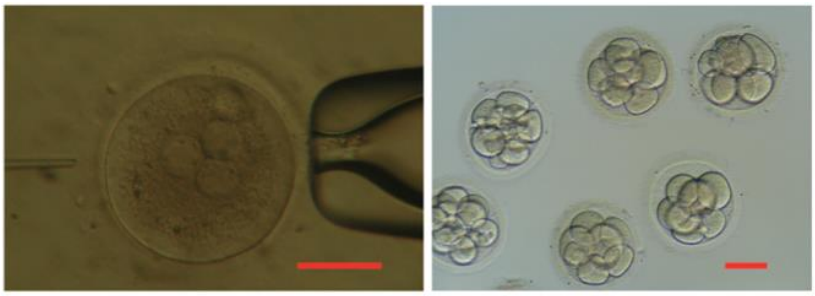
Once the viral DNA copy has been stored, its effectiveness as a defense mechanism is ultimately determined by how thoroughly this 'memory' is transported throughout the cell (Stierwalt). In order to do this most efficiently, copies of the foreign sequences are produced as RNA molecules for their viral search (Sti1). The organism's CRISPR loci present the RNA "encoded" with the viral DNA sequence (Storrs, 2014). The RNA is also responsible for bringing CRISPR-associated (Cas) enzymes to the foreign DNA, travelling around the cell as a unit in pursuit of viral matches. If reinfection with a 'logged' virus occurs and a match is found, the encoded RNA will complementarily bind to the invader's genome. Once the RNA has completed its task, the Cas enzyme performs its duty, cutting the invading DNA to prevent any further replication of the virus. (Storrs)

Naturally, the success of this mechanism in single-celled organisms sparked the quest for potential human applications. It soon was discovered that the multi-cellular CRISPR/Cas system only required two components: a specialized RNA known as guide RNA (gRNA), and a Cas enzyme. (Storrs) gRNA functions in much the same way as bacterial and archaeal cells' CRISPR RNA, despite being shorter in length. After binding to the complementary sequence on the target genome, gRNA works together with the Cas enzyme to find the correct site for DNA cleavage. (Storrs) These striking similarities encouraged scientists to speculate about the new realm of possibilities. This potential became increasingly realistic with the 2012 discovery that the "edit-search-replace" mechanism of the CRISPR-Cas9 system, a pairing of a specifically-programmed RNA molecule and the Cas9 enzyme, was not limited to viral DNA (Sti2). With each additional speculation regarding the generalizability of this technique, the scope seemed to grow exponentially.

The potential application of the CRISPR-Cas system to any gene sequence, and the consequent newfound ability to cleave DNA in a specified location, naturally gave rise to the promise of genomic editing particular genes. (Stierwalt) However, breaking the DNA is only half of the process. Once the DNA has been cleaved, how does the alteration or replacement of a gene occur? There are two primary methods for repair, both reliant on a cell's naturally-occurring repair mechanism. Thus, issues begin to arise in that the products of these repair mechanisms are not nearly as predictable as the CRISPR-Cas systems. The naturally-occurring method is characterized by the introduction of mutations, resulting in the inactivation of the gene. The artificial method, however, includes the insertion of a plasmid containing the new gene for modification. Regardless of the method performed, a great deal of the post-breakage DNA annealing is dictated by chance. Once the co-injection of the CRISPR-Cas cocktail and the

new gene has occurred, as depicted in **Figure 1** below, we have little control over how the DNA precisely anneals after a breakage. It is simply determined by the DNA whether or not the desired gene gets recombined. This unfortunate reality of this 'part 2,' in **Figure 2,** of the genome editing process explains the potential for low success rate of recombination, and introduces the potential for numerous ethical concerns to arise.

(a)



(b)

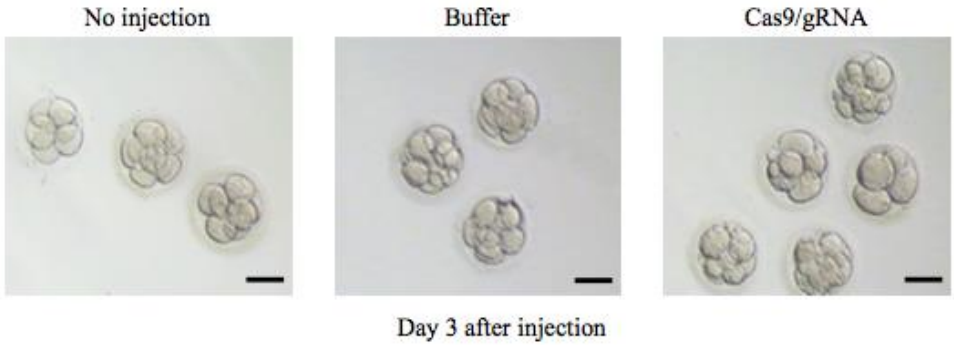
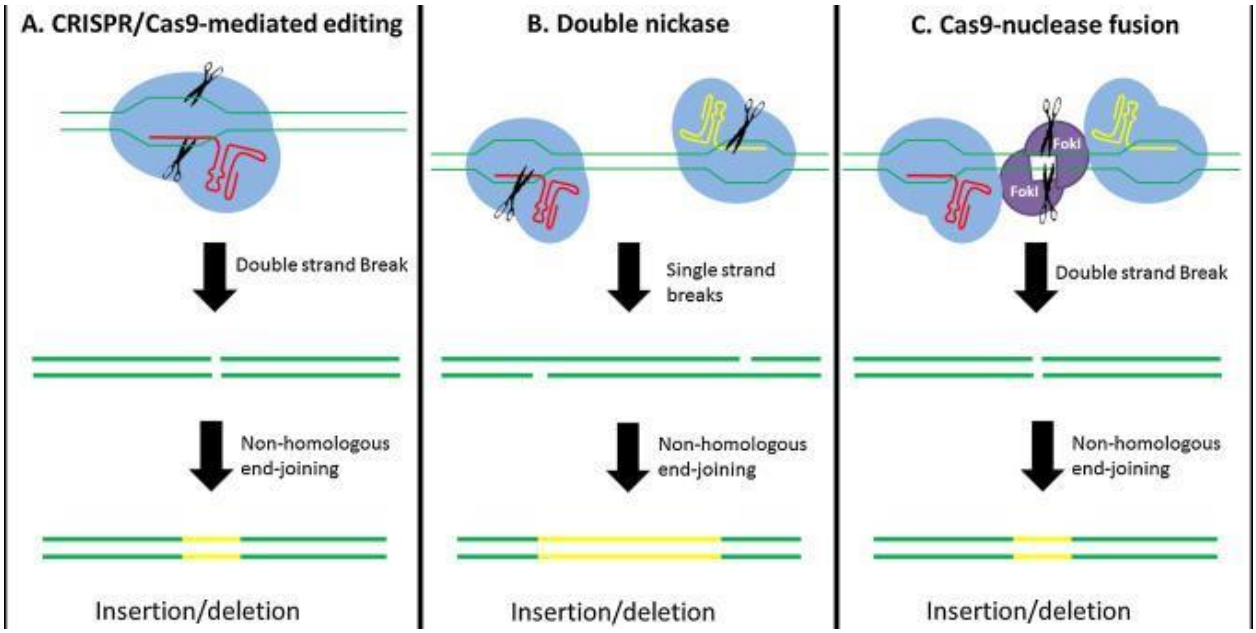


Figure 1. (a)(b) Co-injection of CRISPR-Cas9 cocktail and new form of gene.



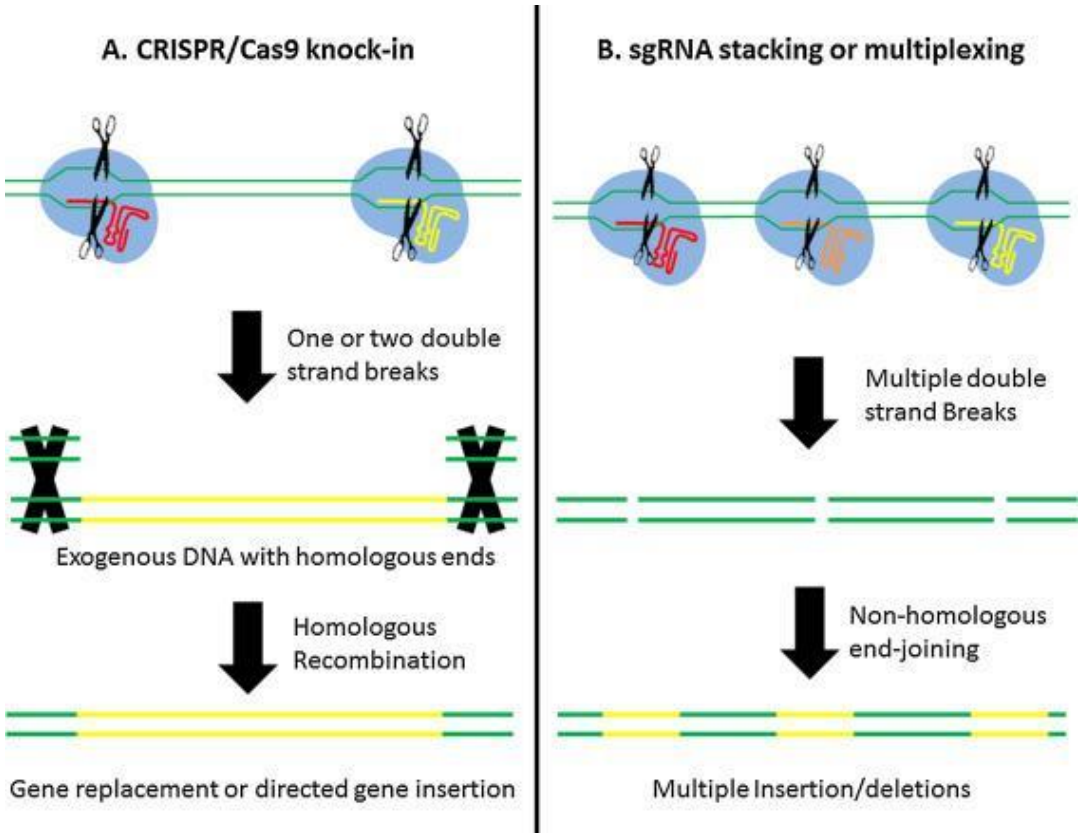


Figure 2. (a/b) Mechanisms of gene addition, creating recombinant DNA with the new gene.

Imperfect vs. Perfect CRISPR

One must not forget that, though this technology seems infallible with its roots as an organism's natural immune system, this is not the case. At times, gRNA can bind to DNA targets that have sometimes several mismatches, meaning the target is only *partially* complementary ("Genome-CRISP™ CRISPR Products and Services." (n.d.)., Storrs). This phenomenon results in one of the larger issues of CRISPR, its "propensity to cause what is known as off-target indel mutations." These modifications can have an effect on the products of CRISPR, like for gene therapy or even full organisms, and can also result in the development of cancer (Obasogie, O. K., & M. Darnovsky (2018)). CRISPR has also been known to cause errors in editing. One example is the failure of *all* embryonic cells to absorb the desired alterations in DNA, a phenomenon known as mosaicism. (Connor, 2017)

If this technology has the potential to create a human being with the unintended effects, innumerable ethical implications begin to arise. There is already extensive disagreement as to whether we should possess the qualification to create any life in this manner. This prospect adds an additional layer of complication when this life may be deprived of a multitude of rights at the hands of fallible humans toying with science. Creating an individual with deficits that make them less fit for survival from the start, without any regard for their consent, seems utterly irresponsible and unethical.

There have been several proposals of how to fix this off-target modification issue with CRISPR. A mutant form of the normal Cas9 enzyme, Cas9 D10A "nickase", is not able to fully cleave through the double-stranded DNA, rather it just creates a "nick" by only cutting one strand of the DNA. If two sgRNA molecules bind to opposite strands of the target DNA, two mutant enzymes each create a 'nick' in the respective strand they are brought to, creating a

‘staggered-cut DSB’. This cut is able to be fixed by NHEJ or HR. This technique has been demonstrated to greatly reduce the frequency of the off-target modification dilemma often seen with CRISPR (“Genome-CRISP™”).

However, this technology still does not completely rid the change of off-target indel formation from occurring, and there are several other hindrances with the use of double nickases. Primarily, their use is hindered by the fundamental constraints of design in that the guide gRNAs must be on opposite strands, in opposite orientation, and display optimal activity when spaced from 3-20 nucleotides apart. Additionally, these nickases tend to produce lower cleavage activity than the typical Cas9-gRNA. (“Genome-CRISP™”) However, Mitalipov and his colleagues are sure that, because we are aware of these common errors in CRISPR, they can be avoided. (Connor)

The ultimate test of the ethics is to consider the prospect of genome editing if the potential for mistakes was completely eliminated. If these techniques were guaranteed to be 100% effective, efficient, and safe, does this remove the ethical implications of genome editing, or is it still unethical? Does this change the way humans should use this technology? This also reiterates the previous discussion that, with regard to which genome editing technique used, the ethical questions are technology-independent.

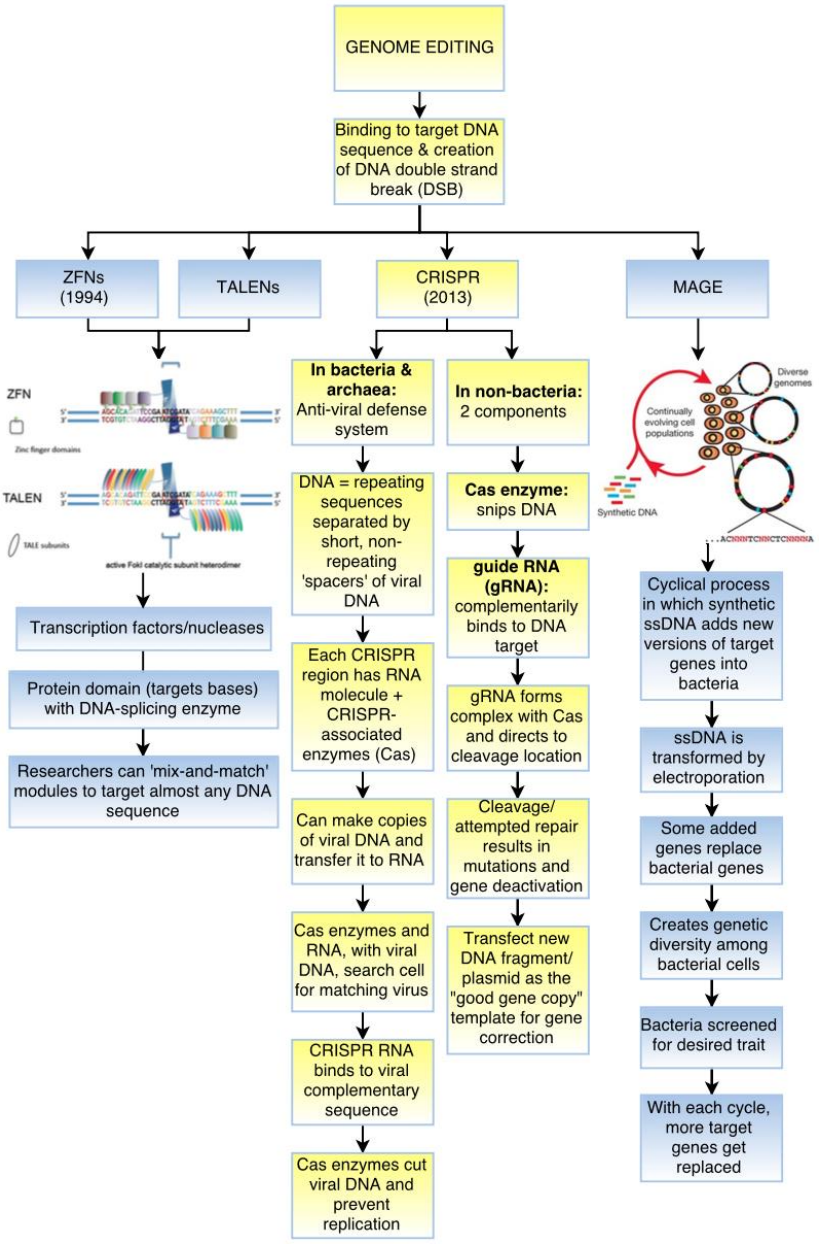


Figure 3. The commonalities and unique mechanisms of each genome editing technique.

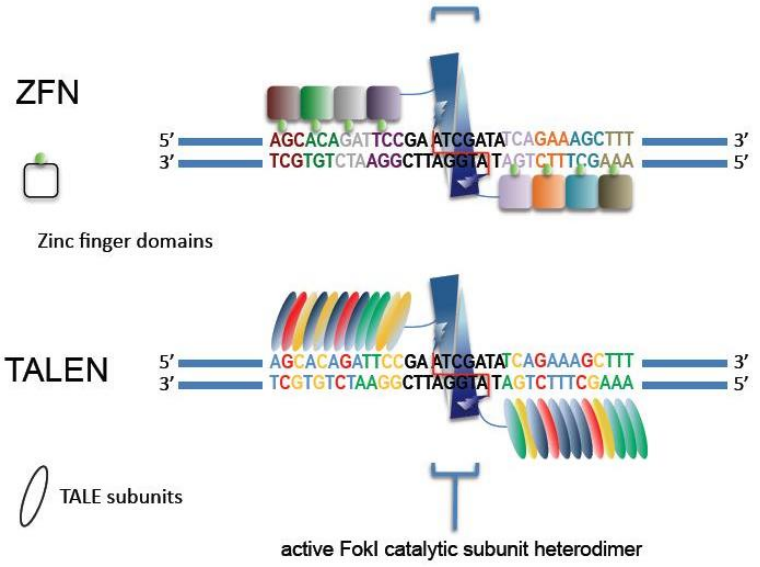
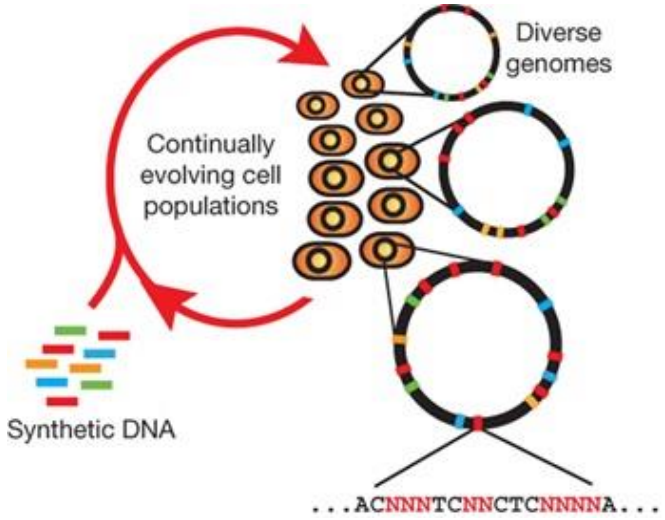


Figure 4. (a) Enlarged Figure 2 image of ZFN and TALEN mechanism



(b) Enlarged Figure 2 image of MAGE mechanism

Why CRISPR?

At the onset of this composition, I promised an explanation to a question that has likely received thorough deliberation by this juncture. If there are four techniques available and used for genome editing, why have I chosen to devote an entire thesis to CRISPR, especially if it is not the newest technique? An introductory overview of the available techniques, provided

above, will be beneficial. **Figure 4a** and **4b** provide the enlarged pictorial elements of **Figure 3** for a clearer viewing.

As evidenced in **Figure 3**, ZFNs, TALENs, CRISPR, and MAGE unanimously share a crucial commonality in the fundamentals of genetic engineering; namely, each technique relies on enzyme specificity to target a particular region of DNA and create a break in the double-stranded molecule. The subsequent branching of this commonality, however, denotes that the similarities among techniques only extend so far. While an entire additional thesis could be composed on these differences between, and the appropriate applications of, each genome editing technique, the CRISPR-Cas9 system will be the primary focus of the analysis to follow for the subsequently discussed reasons.

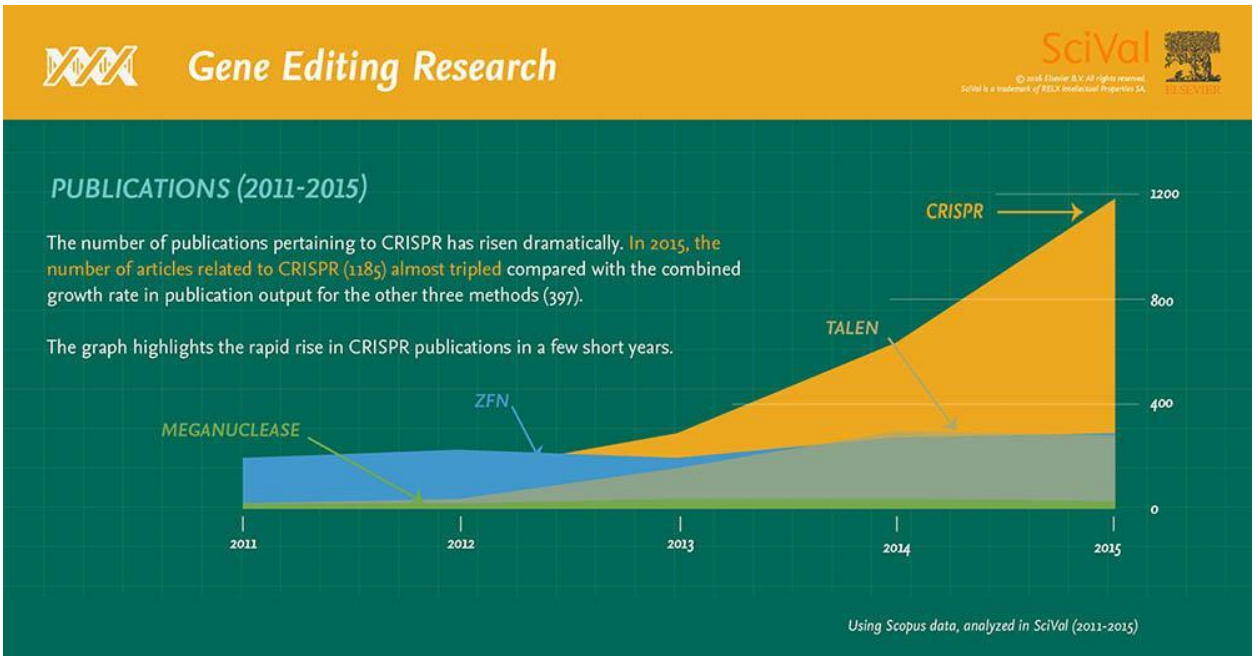


Figure 5. A graphical comparison of the number of publications, from 2011-2015, for each genome editing technique.

The answer is, quite simply, evidenced by **Figure 5** above. To reiterate the most staggering notation for emphasis: "In 2015, the number of articles related to CRISPR (1185) almost tripled compared with the combined growth rate in publication output for the other three methods (397)" (SciVal). CRISPR's current frequency of use, with increasing frequency anticipated, epitomizes why it is certainly the most qualified for this discussion, in a variety of categories.

As one could likely assume from the staggering numbers above, CRISPR has successfully been adopted by pop culture. This feat, while providing further evidence that it is the correctly-chosen technique in order to reach the largest audience, also has its share of detriments. Likely due to its incorporation into various movies and television series, both of which exaggerate by nature, much of the pop culture buzz surrounding CRISPR technology is incredibly far-fetched. Reality grows immensely out of proportion as the media and films proliferate the attention-seeking elements and suppress the truthful ones.

While it may not affirm the scientific basis of why CRISPR was selected for analysis, it is worthy to note that its name is even becoming the coined term for the broad field of genome editing. If an individual says the brand name, Kleenex, it would be clear that they are simply referring to a tissue of any brand. In the same way, it has become a common occurrence to simply say 'CRISPR' to refer to genetic engineering as a whole, and if you mention 'CRISPR,' most would understand to what you are referring. The mention of ZFNs or TALENs, however, may not. This observation provides further confirmation of the increasing commonality of CRISPR technology, a trend that is certainly going to continue as more research is completed and its effectiveness is perfected.

MAGE's title as the newest available genome editing technologies may, understandably, induce the argument that it must be the best technique. However, to this I would like to present the counterargument that, because of its recent discovery, significantly less information is known, and fewer studies display its use; thus, I believe it would yield a far less complete analysis. It may also be tempting to exalt the use of ZFNs or TALENs due to their ability to recognize and target larger portions of DNA. However, because these molecules are "fusions of a nuclease enzyme and DNA-binding domain protein," these techniques present difficulties for cloning and cellular expression (Storrs). Additionally, it can be challenging to find the particular ZFNs and TALENs that recognize the desired DNA-binding domain. Thus, the use of either technique, likely to require the testing of dozens of ZFNs and TALENs, can prove to be a both tedious and costly undertaking (Storrs). Each technique, indisputably, has particular advantages that outweigh those of another technique in a given scenario. CRISPR presents the greatest overall advantage in that: 1) its more recent discovery improves upon particular issues demonstrated by earlier techniques, 2) it is better understood and more researched than the most recent technique, and, finally, 3) its cultural presence and recognition enhances the influential nature and reach of literature discussing its implications. Ultimately, CRISPR technique lies in the 'sweet spot' of being the most current of the well-understood techniques, and its effectiveness in various applications continues to rapidly improve (Storrs).

Despite the purposeful decision discussed above, it is vital to recognize that, ultimately, the specific technology chosen for this analysis does not affect the ethics of the matter at hand. The ethical analysis does not hinge on a specific technique, as they all boil down to the same ethical considerations of toying with the natural order of human creation. CRISPR, for the reasons explored above, simply serves as a well-qualified representation of any genome editing

technique, previously discovered or of the future. The overarching implications that genetic engineering will have on society, regardless of the technique through which it occurs, are ultimately identical. Any technique, past or future, begs and will beg the same questions that we must bring to light in a society where they are currently in the dark shadows, cast by anticipation of what lies ahead.

Applications of CRISPR

Genome editing may still be in its premature stages for human beings, innumerable instances of successful engineering have been documented in various other organisms. One such example was a study conducted at Northwest A&F University in Shaanxi, China, inspired by the increasing occurrence of bacterial-caused tuberculosis (TB) in cattle, and other mammals, world-wide. The grave nature of this infection is namely it is a common food source, affecting any cow product for consumption, and the infection of other animals. In attempts to produce viable cattle that demonstrated resistance to TB, researchers inserted the 'tuberculosis resistance gene *NRAMP1*' into the genome of the cattle subjects. When the 'resistant' cattle produced calves, they were live and "show[ed] signs of increased [TB] resistance" as well. While there is some disagreement that this is indisputable evidence for TB-resistant cattle, the successful identification and insertion of a resistance gene undoubtedly lays the foundation for generalization to other infection resistances ("Tuberculosis-resistant cows developed for the first time using CRISPR gene-editing technology" (n.d.)).

An additional example worthy of analysis is known as the 'Beethoven mouse model' (Olena, 2017). The inner ear contains hair cells that detect the sound waves from auditory stimuli, whose function the gene *Tmc1* is responsible. A dominant mutation in this gene thus results in progressive hearing impairment due to the death of these hair cells, typically beginning

in childhood. The appropriately-named model demonstrated that, in the mouse version of the *Tmc1* gene, a point mutation in the same location as on the human gene resulted in the commencement of hearing loss at three weeks, and complete hearing loss by eight weeks. The impairment is an autosomal-dominant trait, so newborn mice with one mutant 'Beethoven allele' and one wild-type, or normal, allele were the subjects of this test. The CRISPR technology was injected into the inner ear of one ear, leaving the other as a control for comparison. After eight weeks, the ears that did not receive treatment displayed "rapid hair cell death," while those that were treated possessed "healthy hair cells" (Olena).

While the result of this study proves promising for members of the hearing-impaired community due to this mutation, the mechanism by which they performed this transformation is what will likely lead to its broader use for various other forms of genome engineering. Though David Liu and his fellow researchers implemented a fairly typical CRISPR gRNA-Cas9 complex system, no "virus-based system" was used for its delivery. Thus, they were not forced to "rely on persistent viral infection" (Olena). Instead, the complex system was "encapsulated" within lipids to create a ribonucleotide protein (RNP)-lipid complex, improving "editing selectivity" for the mutant allele. Because the trait at hand is autosomal-dominant, guide RNA was able to target the mutant gene, or the infectious gene copy, which eliminated the overshadowing of the normal, recessive allele. Due to the enhanced selectivity, the mutant allele "was targeted 20 times more often than the wild-type allele in cultures of mouse fibroblasts" (Olena). This RNP technique is one possible solution to the off-target effects commonly associated with genome edits performed by CRISPR. The direct, local injection for RNP delivery provides an additional advantage for areas that can be physically reached by this technique, such as the eye and ear tissue, and is significant for the future advancements of such techniques.

The CRISPR-Cas9 technique also is proving to hold promise for a variety of diseases of the nervous system, based on a study performed on mice with Amyotrophic Lateral Sclerosis (ALS). Also known as Lou Gehrig's disease, ALS is a condition for which there is presently no effective long-term treatment, and is the result of a variety of mutations, one of which is a dominant mutation in the *SOD1* gene. This gene "encodes superoxide dismutase 1", which typically "protects cells against toxic free radicals" (Zimmer, 2017). Muscle deterioration, eventual paralysis, and death are often caused by this mutation that results in the "premature death of motor neurons in the brainstem and spinal cord." (Zimmer) In an attempt to not only mitigate the *SOD1* mutation but also the neuronal damage it causes, Schaffer and his research team delivered two crucial molecular elements into an ALS mouse model - "a gene encoding a Cas9 protein designed to excise the *SOD1* gene," and a virus that is able to serve as a vector into the spinal cord's "nuclei of affected motor neurons." (Zimmer) The mice that received this treatment had a "thirty-seven percent delay in disease onset, a twenty-five percent increase in survival, and lived about one month longer than the untreated animals." (Zimmer) Though this may not seem to be an improvement significant enough for excitement quite yet, even the small improvements are indications that the research is tracking toward success. Further, the purpose of including studies of this sort is not to argue that these changes are going to impact tomorrow; rather, that steps, though they may be small, were taken and that, with time and continued research, these steps will reach the finish-line of that eventual day in our future, where this technology is a reality.

Though this technology has not been exploited nearly as extensively with the human genome, we must not overlook what has been achieved thus far. The successful application of CRISPR has already been able to successfully wipe out infections like HIV and Hepatitis B from

the genomes in human cells (Stierwalt (n.d.)). Just within the past year, the rapid advancement of knowledge and technology has enabled the progression from genetically engineering human cells to human embryos (Stierwalt). In August 2017, a ground-breaking study was published regarding a team of Oregon Health and Science University researchers who successfully implemented CRISPR-Cas9 editing in human "preimplantation embryos" (Ma, et al., 2017). A critical technique was developed, allowing them to target and correct the heterozygous *MYBPC3* mutation associated with hypertrophic cardiomyopathy (HCM), a condition that causes cardiac muscle thickening and potential heart failure. HCM is the condition most commonly known for causing the sudden death of young, seemingly fit athletes. Using sperm from carriers and eggs from non-carriers, application of CRISPR-Cas9 occurred male gametes as they were injected into eggs. Double-strand breaks (DSBs) were created "at the mutant paternal allele" and, in the creation of the embryos, "were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template." (Ma, et al) Of the fifty-four human embryos, Hong Ma and her team successfully edited thirty-six of them, a feat that had only previously been completed on "immature embryos that were not capable of surviving until birth." (Stierwalt)

While this study, like the others, contributes to the prospect of eliminating disease-inducing mutation, it deserves additional consideration for a particularly novel achievement; one that, arguably, has even greater implications for the future trajectory of genetic engineering. Not only did they demonstrate the ability to correct mutations, but also that this process can simultaneously occur with the creation of a human preimplantation embryo. This team was also able to successfully recognize and avoid many of the common obstacles associated with CRISPR, which are often the demise of fellow CRISPR researchers. The successful creation of genetically-engineered embryos was due to the simultaneous "addition of the CRISPR-Cas9 to

the egg at the same time as the sperm rather than hours later as had been done in previous studies" (Stierwalt). They were able to avoid mosaicism and off-target mutations, common issues that will be discussed further in the pages to follow, through regulation of what stage in the cell cycle it was in when CRISPR-Cas9 created the DSB (Ma, et al). Finally, to avoid the chance that the CRISPR-Cas9 system would remain present and cause edits after the desired changes were complete, they astutely implemented a transient version of CRISPR (Stierwalt).

While these articles, and the many others that exist, share the obvious commonality of CRISPR-Cas9 application, there is also another significant trend that can be easily overlooked in the midst of all of the excitement regarding what the future holds for this technology. Each article contains at least one line that addresses the current imperfection of, or the hesitation to truly accept, the techniques being discussed. Ian McConnell, a University of Cambridge veterinary science professor, exhibits this equivocality, calling the TB resistance technique "'thorough and novel,'" balanced by his skepticism of disease-resistant offspring, calling the in vivo evidence "'indirect'" ("Tuberculosis-resistant cows…"). He goes on to note that, while it is beneficial, the insertion of a transgene is not the single factor contributing to disease resistance. The coauthor of the ALS mice study, David Schaffer, was also not coy about sharing the truth that the treatment performed still did not make the ALS mice "'normal'" and is '"not yet a cure'". Eric Topol, a Scripps Research Institute geneticist, also comments on the study that the treatment used is unfortunately only relevant to a small sector of individuals with ALS - twenty percent of inherited forms, and two percent of all cases. Yet he was just as equivocal as McConnell, following his humble shortcomings with a declaration of his optimism that "'the results were nonetheless encouraging with many positive neurological signs and delayed onset'" (Zimmer).

Several scientists not involved in the 'Beethoven mouse' study shared the shortcomings of the present technology, as well. Primarily, while this was a step in the right direction, inactivation of the mutant gene only partly absolved hearing loss. Using auditory brainstem responses (ABRs) to test the neuronal reactions stimulated by sound in the treated and untreated ears of four-week-old Beethoven mice, and the ears of wild-type mice, "untreated ears registered ABRs around seventy-five to eighty decibels, comparable in volume to a garbage disposal." (Olena) They found that wild-type mice were able to detect sounds of thirty to forty decibels. Beethoven mice with treated ears could hear sounds similar to a quiet conversation, around 60 decibels, which is significantly better than the untreated ears, yet still not to the wild-type hearing. The same testing in eight-week-old mice revealed that, despite genome editing treatment, the treated-ear auditory thresholds nonetheless deteriorated with time, as ABRs for treated ears of eight-week-old mice were "still lower than in untreated ears, but higher than at four weeks." Ulrich Müller, a neuroscientist at John Hopkins School of Medicine, expresses an additional concern regarding the generalizability of the study. The mutation in *Tmc1* is a heritable condition that, for humans, proving itself early in development, which he explains could pose challenges for the successful RNP delivery. (Olena)

Yet despite the current imperfection of these technologies, these articles are balanced with the promise of the path that these advances are travelling quickly on. The ABR threshold of CRISPR/RNP-treated mice may have been lower still than that of wild-type mice, but the underlying editing mechanism was indeed successful. Oregon Health and Science University sensory biologist Peter Barr-Gillespie argues that even such gains of "ten to fifteen decibels could make a huge difference" in the quality of life for hearing-impaired individuals. (Olena) David Schaffer intends to build upon the success of his viral vector by creating an "a highly

modified adeno-associated virus, or AAV, that not only targets motor neurons, but other cells that appear to harm them." (Olena) He believes that the ability to rid the neurons, astrocytes, and supporting glia of *SOD1* will be critical in ALS patients for longer lives. He follows his admittance, mentioned above, with a statement that perfectly epitomizes the ultimate lesson from this discussion. Focusing less on the fact that his study, and others, are not cures for these diseases, he shares that they are "'a really strong proof of concept.'" (Olena) While the techniques may have some refinement to go through, the technology is here and laying the foundation for the eventual perfection of these techniques.

In the Child's Best Interests?

I would feel less obliged to compose this particular thesis if I believed that the ethical permissibility of genetic engineering imposed no threat to society as a whole. Ultimately, however, these weighty decisions fall into the hands of individuals who intend to create a designer human life and to whom this technology is available. The conception of a child is ideally preceded by at least slight parental consideration of the provisions that will be necessary for, at the minimum level, sustenance of life. More thoughtful consideration yields a discussion of issues beyond the fundamental needs. *Do we agree on how the child should be raised with regard to religion, education, and discipline? What will the role of each parent be in this child's life?* However, even those that seem fully prepared likely fail to consider how the combination of particular traits could impact the future of their child. *This* is the premise of the new technology.

Suppose that a parent concedes that, as much as possible, leaving room for natural human error, the intentional choices (s)he makes for his or her child are intended to be in the child's best

interests. Thus, is this concept of choosing advantageous traits, or eliminating deleterious ones, simply an extension of making choices that are in the best interests of your child?

Julian Savulescu, an Australian philosopher and bioethicist, takes this stance a step further. He argues that "we have a *moral* obligation or *moral* reason to enhance ourselves and our children." (Savulescu, n.d.) In his 2001 publication entitled, "Procreative Beneficence: Why We Should Select the Best Children," Savulescu coins this term in his title. 'Procreative beneficence', he defines, is the principle that "couples (or single reproducers) should select the child, of the possible children they could have, who is expected to have the best life, or at least as good a life as the others, based on the relevant, available information" (Savulescu, 2001). Further, "if we have an obligation to treat and prevent disease, we have an obligation to try to manipulate these characteristics to give an individual the best opportunity of the best life" (Savulescu). Most would agree that we have an obligation to treat and prevent disease in an individual on this planet, and would consider it cruelty if we did not. In the opinion of Savulescu, why would we not take care of the remote possibility before it is an issue?

I must propose a set of philosophical arguments that may affect the level of moral conviction to consider the genetic engineering of their children. One argument exists that this concept of a child having a right to an "open future" is meaningless and does not truly exist because we are a product of our environment from the moment we are born into a family. Simply by their sole existence, parents inadvertently exert countless influences on their children. Thus, one parental choice argument may be as follows: if our environment defines us, even if we choose to trait-select, our parents and environment make us who we are anyway. What would the point of genetic engineering be if so many factors can change who we are? A parent under this impression would likely have less conviction to go through the effort and pay the cost to

have designer babies, if they are simply going to be changed by the world. Savulescu presents the alternate argument in his statement, "you will never turn a chihuahua into a doberman through grooming, training, and affection" (Savulescu). In essence, he discounts the level of environmental influence exerted by the factors discussed in the alternate viewpoint is simply never going to cause a drastic change over one's genetic phenotype. A parent who is taken by Savulescu's point of view, not surprisingly, would see the value in trait selection under the notion that genetics will always overpower environmental influences.

In his composition, *The Case Against Perfection*, Michael Sandel addresses an additional viewpoint of this 'open future' argument. He presents the position that selection of genetic makeup of a child in advance, in essence, denies this child a right to an open future. He continues that, in reality, "any form of bioengineering that allows parents to select or reject genetic characteristics" presents the same notion of automatically determining these factors for the child before he or she even enters the world. For example, any enhancement made to make a child more musically-inclined, or more athletic, for example, would inherently skew the child's direction of interests to be these choices; thus, Sandel argues, "designer children would never be fully free." (Sandel, 2004)

What is the "Best" Life'?

If a survey were taken of ninety-year-old individuals - writers, scientists, artists, physicians, musicians, billionaires, missionaries, travel-enthusiasts, to name a few - asking them if they felt that they had lived 'the best life' and why, there would be many who answer *yes,* yet few for the same reasons. So what really are the qualifying characteristics for 'the best life?' Whose opinion ultimately is the deciding factor?

It is also fairly certain that this survey includes individuals who have various clinical conditions, yet still responded *yes*. While I would agree that no parent would ever wish a debilitating condition upon their child, or their family, I believe further discussion is necessary to determine whether a life without these traits is 'the best life.' A study published by *Pediatrics* found that, of the 332 families who returned the questionnaires, ninety-seven percent of families with severely-disabled children reported their child as 'happy' and that, as parents, their lives as parents were enriched because of their disabled child. (Janvier, 2012)

In his argument for trait selection, Savulescu notes that "we want to be happy, not just healthy people." Yet ninety-seven percent of the individuals included in the survey reported their disabled child as happy. It seems that the opinions of those who would know best nullify Savulescu's stance on what truly yields 'the best life.' I agree with the notion that we want more for our children than health. We do want happiness, which may mean the ability to achieve. Yet, I wonder, is achievement necessarily based on traits that can be selected for in a designer baby? I do not feel that I can fully agree that creating a designer baby with selected traits that would yield Savulescu's opinion of a "happy" person, like the lack of disease, outweighs the survey parents' opinion of a "happy" person with joy, despite a disease. Disabled children, as I believe the study's results demonstrate, are often described as achieving higher levels of attributes such as courage, genuineness, and joy than an individual who is considered happy and healthy by society's standards. Ultimately, based on a reflection of the questions posed above, it is the parent's choice of what they believe will give their child a more fulfilled life.

The Degree of Ethical Concern

Figure 6. Depiction of potential outcome examples from genetic engineering, with CRISPR central to depict the tension of outcomes

Intelligence and sex selection: the two traits Savulescu declares to be his focus as he begins *Procreative Beneficence: Why We Should Select the Best Children.* I find it particularly intriguing that the traits he discusses, stated boldly, are those that, based on personal research, would induce a greater degree of disagreement. The culmination of this research is reflected within **Figure 6.** At the risk of making a false assumption for the sake of argument, I would expect that, regarding the acceptable use of genetic selection, more individuals would be in favor

of selection to reduce risk of genetic disease, prevent the transmission of deleterious genes, and better understand genetics. Conversely, more individuals would tend to be against selection that would worsen social gaps, encourage selfish parental motives, or cause feelings of conflict for children. The gray areas, such as self-esteem and what traits are 'necessary' versus 'desired', however, are more likely to elicit disagreement. These varying levels of agreement and disagreement, elicited by the prospect of modification of a particular trait or characteristic, is what I will call 'the degree of ethical concern.' The subjectivity of this distinction, and the innumerable factors on which this decision could be based, is the reason I am able to compose the lengthy prose at hand. *What exactly is a 'benign' trait? Or a 'deleterious' trait? One that yields a clinical condition? Or simply any factor that could hinder an individual in some way?* Of course, there is no unanimous answer for society. The immense ramifications that society, nonetheless, imparts on the parental decision, however, is far from unanimous, as reflected in the following pages.

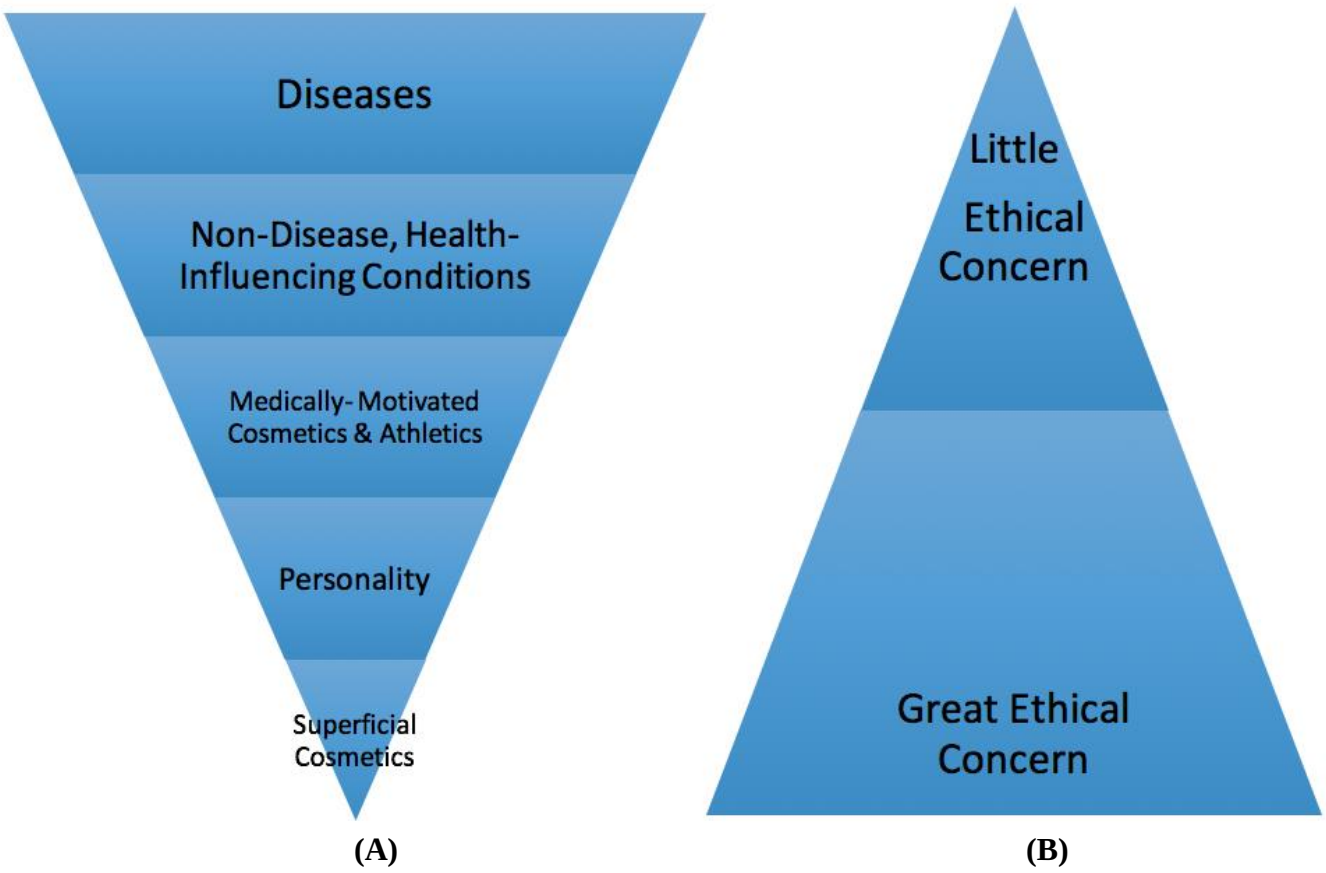


Figure 7. The degree of ethical concern associated with the modification of various traits and characteristics, where traits/characteristics are ranked according to the perspective that, the greater the disagreement for its modification, the greater the ethical concern.

To better understand this 'degree of ethical concern,' it may be beneficial to visualize the 'levels' of traits and characteristics for which genome editing could be used. At the risk of making false assumptions, once again, for the sake of argument, I have constructed **Figure 7** above, based on significant research of popular perspectives. The blue set of triangles represent the degree of ethical concern associated with the modification of particular traits or characteristics, based on the hypothesized *degree of disagreement* its modification is likely to elicit. Several alternate perspectives, which alter the ranking of these traits, will be discussed below.

Triangle (A) depicts traits or characteristics that could hypothetically be subject to genetic engineering, ordered by research-inspired perceptions of society's levels of disagreement regarding modification. Triangle (B) represents the research-inspired perceptions of the degree of ethical concern regarding modification. When traits/characteristics are organized in this way, an intriguing pattern arises. The widest point of (A), representing the trait/characteristic most universally-accepted for editing, corresponds with the smallest point on (B), representing the least degree of concern for using genome editing technology for its modification. As (A) descends, becoming increasingly narrow, the traits/characteristics occupying each consecutive level are less likely to be agreed upon and, thus, yield a greater amount of ethical concern in (B). It would follow that, as you go down (A) and increase the amount of ethical objection that each trait/characteristic is likely to elicit, increased justification is required to explain its position.

Based on the prescribed logic, engineering for disease-causing agents occupies the level with widest degree of acceptance, and aligns with the least degree of ethical objection. The level below disease in (A) would be a trait/characteristic that may not, at least presently, be considered a clinical disease, but, nonetheless, has significant implications for one's health. Obesity, for example, would fit in this level of traits/characteristics. It follows logically that obesity would receive slightly more ethical resistance than diseases because the latter is more universally-accepted to be a trait defined by genetics, and subject to little-to-no change based on lifestyle. Obesity, though there is increasing evidence that it is rooted in genetics, there is, nonetheless, an increased amount of personal choice and responsibility associated with such a characteristic. Thus, fewer would likely feel inclined to prioritize the elimination of this trait by genetic engineering, compared to a disease that cannot be prevented.

Descending through (A), we can even begin to differentiate between sectors of a particular trait/characteristics. Cosmetic enhancements through genetic engineering, for example, can be divided into 'medically-motivated' cosmetics and 'superficial' cosmetics. Medically-motivated cosmetics occupy the next level below obesity, as these are traits/characteristics that can impact health, yet are still cosmetic. For example, genome editing to prevent Cleft Palate that causes difficulty eating or drinking, but does not impact health as severely as the traits/characteristics above, and could potentially be a desired fix for simply cosmetic reasons, would be medically-motivated cosmetics. An additional trait/characteristic that is appropriate for this category is athletic ability. While athletic ability may enhance your fitness and health, an individual does not absolutely need to be athletic to get exercise, as anyone is able to walk. However, not everyone might agree with this and some may feel that selecting for athletic ability is more, or less, worthy than another trait/characteristic, potentially depending on personal values, which explains its intermediate position in (A).

Personality traits occupy the next level of (A), in which selection of these traits has no impact on overall health. However, overall *well-being* could be influenced by your demeanor and, thus, how people respond to your presence. An individual with a friendly personality is likely to elicit a better response from others, which could make one feel more in harmony with others, or help get the better job based on interview skills. Though these traits do not have health implications like diseases, they likely earn less ethical debate than superficial cosmetic traits because they have potentially legitimate impacts versus those based completely on subjectivity. Yet even the terms *good* and *bad* to describe personality are very much subject to interpretation and challenging to agree upon. They may even be subject to cultural interpretations. This controversial nature explains why personality traits occupy a level close to the bottom of (A).

However, the likelihood of a consensus on what is a *good* versus *bad* personality trait is greater than that for superficial cosmetic traits, earning these traits the base of (A).

Superficial cosmetics occupies the smallest region of (A), denoting the largest causation of ethical debate for its modification. These traits also have no influence on overall health. However, overall well-being could, once again, be influenced based solely on personal preference and is, thus, the most controversial, corresponding to the broad base of (B). When genetic selection occurs based on preferences, or current standards of 'what is the best' according to societal values, the solid grounds for the decision dissipates. Selection of traits such as height, musculature, eye color, or skin complexion is likely influenced by what society and the culture think are best, which can change very quickly, like any other fad. However, height poses an interesting conflict in that being short is not a disease, but some parents may choose to select against it because being tall is correlated with greater success in our society, as discussed in further detail below. Further, one could argue that determination of success in a career is not superficial, and has far greater implications for who you become as an individual than the other traits in this level. Thus, as expected at the base of (B), the confusion is great for determining traits that genuinely impact an individual's success, versus those based on personal opinion. If society permits selection of traits that have no impact on the health and are subject to humans attempting to define perfection for ultimately no legitimate reasons, this is the foundation of what ethicists call *a slippery slope*.

The slippery slope argument is very powerful in such situations where fine lines are being drawn between what is and is not permitted. As seen in **Figure 8**, if we have morally-permissible Moral Action (A) and unethical Moral Action (B), the slippery slope argument states that if A.1 happens, and then A.2, we will inevitably be brought to do (B). Are (A) and (B)

equivalent? If (B) is wrong, then so is (A). Thus, if justification for (A) could be used to justify (B), then this is a slippery slope).

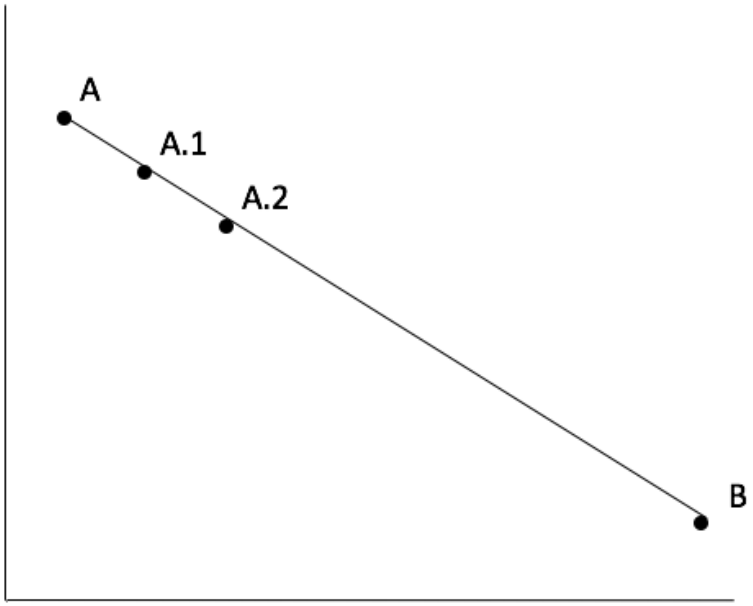


Figure 8. The philosophical slippery slope argument, progressing from A → B.

The amount of overlap and potential justification to switch traits/characteristics among levels is what makes genetic engineering a slippery slope. Under the notion that, if you permit the selection for a trait/characteristic at the top, you may begin to convince yourself that traits/characteristics from the level below are members of the level you feel is morally permissible. Gradually, you begin to accept even the most controversial, least health-influencing traits/characteristics.

For example, an individual may begin with the opinion that genome editing should strictly be used to eliminate disease. Now you and your spouse are sitting in the genetic counselor's office planning for your first child. You skim the checklist in front of you - Diseases, Non-Disease Conditions, Medically-Motivated Cosmetics, Personalities, and Superficial Cosmetics - shaking your head in disapproval as you read the last category. You cross off all

diseases as you had planned to do, but now you realize you have already eliminated the chance for your child to have any genetic disease…why leave in the possibility of him or her becoming obese if you could just as easily give a completely clean slate? So now, if your child will be disease-free, his or her biggest burden that you could impact in that moment is that (s)he will not have to endure the embarrassment you did as an unathletic child in gym class. But now if (s)he is athletic, (s)he's going to want to join a sports team and you, as a normal parent who wants the best for their child, want him or her to be well-liked by teammates. So you start to pick out personality traits, but as you are checking the boxes, you notice your clubbed thumb and remember how often you were teased for it. You think to yourself, 'I would be a terrible parent if I gave my child a feature I know (s)he would be teased for…' Before you know it, you are checking boxes in the section at which you had previously shaken your head.

It is the unfortunate reality that, as you descend in (A), justification for the next level becomes increasingly easier, because even larger ethical objections seem more justifiable when you have justified all levels leading up to it. While it may seem inappropriate to include 'personality' before its genetic basis has been fully determined, its inclusion was intentional in this hypothetical construction. With the combination of decreasing ethical stringency, and increasing sophistication and success of research, I am confident that we will eventually be capable of changing personality and, by this time, many more will gradually grow to find it permissible, by the slippery slope argument. As the impossible become the possible, it becomes increasingly easy to slip down the slope. Thus, if society is fearful enough of what genome editing has potential to become, the ultimate solution may be to avoid its commencement.

If we ask a more narrowly defined question about the ethics of genome editing, the blue triangle figure is most fitting. *Should we encourage the application of genome editing, or*

restrict, prohibit, or even ban it, with respect to the entries listed in the figure for any disease or trait in any person? Here, the ethical debate would be very minimal or non-existent for the prevention and cure of diseases, and massive for 'superficial cosmetic genetics.' If we pose a broader question, however, the debate becomes more complicated, especially with respect to curing and preventing diseases. Who would have access to such editing technologies, and under what specific circumstances? Would all parents have equal access to such powerful genetic methods for ensuring disease-free children, and perhaps children with the 'best' traits? Ultimately, while the blue triangle figure answers the simple and direct question about the ethics of genome editing, it cannot answer the more complicated question of access by privileged groups within any society.

The most realistic triangle model would be interactive and dynamic, so that (A)'s levels could be vertically shifted based on the perspective from which the traits or characteristics are viewed. Rather than re-creating numerous additional diagrams, I will simply explain here that an additional static triangle pair could be constructed for each of the alternate perspectives -- *How much or how little should we interfere with the trait? What is its moral gravity? How much good are we doing by getting rid of a trait? How much harm are we doing by interfering?* Even a perspective that justified moving *superficial cosmetics* from '*least* agreed upon' from one perspective, to '*most* agreed upon', when viewed from the perspective of universal agreement of indications of fertility. The primary purpose of the attempted depiction was not to create the 'correct' ranking, but rather to demonstrate how complex the implications in society for these decisions truly are.

What is the Motivation?

After a discussion of potential traits subject to modification, it follows that the consequent task should be a deeper analysis of an individual's motivation for the selection of particular traits. In the United States, tall stature and extroversion, among others, are widely regarded as superior to their respective alternatives. The consultation of numerous resource's examples has revealed two primary foundations of reasoning: *culture* and *evolution*.

Research has demonstrated that the brain inadvertently associates stature with fitness level and, potentially not as apparent, social status ("Height discrimination", 2018). Independent of cognitive awareness, the brain "associates physical size with leadership potential, power, strength and intelligence," a phenomenon seen in infants as early as 10 months of age, and one that is more evident in men than women. From an evolutionary perspective, taller stature indicates a well-fed individual who is, presumably, of high social status to be able to provide resources. Height has additionally become thought of as an indication of two additional attributes, "general health and physical strength, the latter of which can be useful in asserting dominance." (Height discrimination)

Stated frankly by author of the US bestseller *Quiet: The Power of Introverts in a World That Can't Stop Talking*, Susan Cain, "'society has a cultural bias towards extroverts.'" (Tucker, 2012) Supplementing the stereotypes she breaks with corrected perceptions, she defines introversion and extroversion as "'how you respond to stimulation,'" rather than false tags like 'antisocial' and 'shy'. In an 2012 interview conducted by *The Guardian's* Ian Tucker, Cain shares her opinions on how society came to value extroverted traits over introverted ones. "'Our cultural DNA,'" she states, as "'Western society is based on Greco-Roman ideals of the person that can speak well, a rhetorical ideal'". Though she argues our Western society has always been

one that "'favors action over contemplation,'" the preference for extroversion really took hold in society's transition from the 20th century agricultural society to the business-oriented 21st century. The societal mindset also shifted to believe that, in order "to stand out and succeed in a company, with people that you had never met before," one must be "'very magnetic, very charismatic in a job interview'" (Tucker). It was at this time, too, that cinema's popularity increased, glamorizing the "magnetic and charismatic" movie stars and providing a 'role-model' for introverts; thus, she argues, "'this [mindset] became very deeply ingrained'" (Tucker). In a conversation regarding how work and school environments are geared to the ways extroverts prefer to work, she describes society's current "'value system' as the 'New Groupthink,'" a recipe for creativity that is focused on communication and 'chance encounters' with others, yet "leave[s] very little place for deep thought and for focus,' both 'crucial ingredient[s] for creativity'" (Tucker). Cain also speaks to the evolutionary nature of this societal flaw. She explains the theory that younger individuals experience a greater need to be extroverted in order to find "mates," a pressure that diminishes with age. Thus, "'we get more introverted with time'" due to this deprioritization for evolutionary drive. (Tucker)

Analysis of both trait varieties from a cultural and evolutionary perspective reveals the seemingly simple theme that individuals desire what is perceived as 'better.' What is not obvious, however, evidenced by the intriguing pattern of society's reinforced preferences, is that 'better' might not always be better. If individuals truly desire what is 'better,' there may be reason to believe that parents might not always want to choose tall stature and extroversion when designing their child.

As an 5'2" individual, I feel particularly intrigued by the proposition that there could arguably be more advantages associated with shorter stature. I propose one such advantage to be

that shorter individuals could potentially experience decreased economic pressure. While the prospect may initially seem trivial, even slightly comical, shorter individuals, on average, weigh less, resulting in the less rapid deterioration of furniture and, thus, decreased frequency of replacement. David Mizne's article, published by *15Five*, highlights several characteristics of introverts that differentiate them from their extroverted peers. Introverts possess a thicker prefrontal cortex for increased thoughtfulness and planning, and this tendency to thoroughly process ideas can make them the better public speakers, a concept completely foreign to our society ("Who Performs Better At Work, Introverts Or Extroverts?", 2017).

With these characteristics in mind, Mizne presents an intriguing analysis of which type, introverts or extroverts, make the better leader, and the better employee. In a society where the outgoing, strong communicator is seen as the most valued member of the team, it is no surprise that a University of North Carolina study found that "96% of managers and executives display extroverted characteristics" ("Who Performs Better"). However, a 2016 publication by University of Chicago, Harvard University, and Stanford University researchers categorized over four-thousand CEOs by personality traits, demonstrating that the better leaders were the *introverted* chief executives. Ultimately, "'introverted CEOs outperformed companies ran by extroverts,'" which co-author Steven Kaplan argues is because floundering companies tend to "'seek out a big personality,'" who ultimately "'gets blamed when they can't turn the ship around.'" ("Who Performs Better")

Mizne's subsequent determination of the better employee addresses a significant issue to bear in mind. There are particular jobs that are better completed by introverts, and others that are more suited for extroverts, and both are equally important. As with almost any pair of opposites, there are both advantages and disadvantages associated with each side. In groups that work well

together, extroverts are "energizing force[s];" yet, in situations of disagreement, aggressiveness can actually escalate the conflict. ("Who Performs Better") Introverts, too, possess strengths and weaknesses in that they are more likely to have the thoughtful ideas based in thorough reflection, yet do not thrive, as extroverts do, in social settings. In her interview, Cain mentions an additional benefit of introverts, namely that "'when creativity is the highest priority people should be encouraged to work alone.'" (Tucker)

Why do these traits remain less desired if they, too, have advantages...even ones that solve or outweigh certain issues posed by the societally-deemed 'better' traits? Though, by this juncture, we have certainly witnessed enough large implications to assume the answer to be *the parental reinforcement of these particular values in society*, this does not truly answer the '*why.'* The answer to this question, I believe, is ultimately because we are a species driven by the forces of evolution. This evolutionary mechanism is really only intended to keep an organism alive until it is able to reproduce. It is after this point that what has value and what does not is determined by culture. Height, for example, was, evolutionarily, very important for the survival of early humans. Yet, despite the disappearance of this need, and the transition of height as more cultural, we evidently possess this evolutionary perspective of height. As a result, these traits are subject more to *intrinsic opinions* than rational thought. Our perceptions, right or wrong, are so deeply intrinsic that we need strong introverted individuals, like Susan Cain, to explicitly state that extroversion is not necessarily better for us to truly start to believe it, counteracting this innate mechanism. This notion is frightening enough for individuals, much less for parents who are responsible for selecting 'better' traits for their children with skewed perceptions of what is 'better.'

Traits with No Health Advantage

Hair color. Eye color. Skin color. Face shape. Many more could be added to this list, but the trend becomes apparent after just two or three. These 'superficial' traits, while some of the most important for societal advantage, ultimately have no long-term health advantage. For example, having blonde hair versus black hair, or green eyes versus blue eyes, has no significant correlation to decreased risk for a particular disease. There tends to be a general skepticism regarding selection of 'superficial' traits, a phenomenon likely stemming from concern of a recurrent eugenics movement. Adolf Hitler's implementation of the Aryan race was based on a superficial notion that blonde-haired, blue-eyed individuals were the only members of society worthy of proliferation. His 'random' or 'not- based-on-any-true-genetic-advantage' selection had such devastating effects for those who happened to possess the other 'random,' it would follow that modern selection of these random traits based on personal preference invokes a reminiscent fear.

Such traits were briefly discussed with respect to the degree of ethical concern. Recall that differing perspectives can change the way particular traits or characteristics are ranked with one another. The particular triangle example above, however, ranked traits from the perspective of the elicited level of disagreement regarding the modification of the trait. From this perspective, traits with no health advantage were argued to be the source of the greatest contention, as their level of importance and influence in one's life was 'least agreed upon.' However, the concluding notes of this section presented an alternative perspective responsible for making this same category of traits, now, the 'most agreed upon.' When these superficial traits are universal, subconscious signs of fertility, such as a symmetrical face and small waist,

this evolutionarily-driven agreement allowed superficial traits, from this perspective, the *most* agreed upon.

Ultimately, it seems that each 'degree of ethical concern' scenario above operates under one of two opposing ethical schools of thought on the matter. Those that agree the *least* on the influence of 'superficial' traits resonate with the first school of thought, resistant to the idea of 'superficial' trait selection. They might ask, *Is using this technology for the selection of 'superficial' traits that have no impact on the medical well-being trending on the path to eugenics?* Those who operate on the opposite end of the ethical thought spectrum resonate more with the universal evolutionarily-driven agreement on the influence of these 'superficial' traits. This group, instead, would ask, *Is there anything wrong with interfering, if that is what science and technology have always allowed us to do and we have been doing this for so long already?* With a mindset very trusting of nature and evolution's, ability to maintain the balance between humanity and technology, this society sees no issues with selection of 'superficial' traits. Regardless of an active or inadvertent recognition of his or her preferred school of thought, it is this parental choice to select for 'superficial' traits that reinforces society's view.

Parental Motives, Expectations, and Disappointments

One of the most detrimental effects of this technology is one that can occur in the absence of any conscious realization. The product of idealization constructed by the human mind inevitably leads to disappointment. With the infiltration of this life-creating technology, there will be a transition from gratitude to disappointment. When parents embark the journey of bringing a child into the world with no preconceived notions, there is a natural sense of gratitude for any combination of traits this child will have. Yet when specific traits are consciously chosen over others, it is human nature to imagine the best possible outcome of the chosen traits.

Suddenly the exhilaration of surprise becomes disappointment, intentional or not, based on the expectations perfected by nine months of mental fine-tuning.

We must also view this dilemma from the perspective of the designer child. Children observe and internalize every interaction and occurrence, particularly of their parents. If a child perceives parental disappointment based on his or her failure to align precisely with the preconceived image, one can only imagine what effects this will have on not only the child, but on society as a whole. It may also be the case that a child develops this realization independently, wondering why his or her parents felt that they would not love him or her as a non-designer baby in the same way and, thus, resorted to technology for his or her creation. A generation of children who feel unappreciated will develop self-esteem issues that translate into a tendency toward a variety of negative behaviors. While the traits are thought to make these individuals more apt, beneath the perfect surface, it may be the resulting issues that cannot be fixed with genome editing that prove to be disqualifying.

In attempts to nullify the concern regarding a designer baby's feelings of failure to conform to the preconceived image, one may argue that a girl born to a family of all girls hoping for a boy, or vice versa, could result in these same feelings. While I think this could potentially be true to a very small extent, I do not think the extent to which it occurs in this contemporary situation is even slightly comparable to a designer baby. I believe the random, fifty-fifty chance of having either gender, which the parents did not intentionally selected for, creates significantly less parental feelings of expectation. It also creates significantly less feelings of unwantedness for the child in comparison to a designer child, who is aware that his or her parents intentionally desired to select of specific traits and did not receive them. Ultimately, the difference between the notion that parents who are surprised by the gender could still be happy with what they

receive, and the notion that parents who specifically did not get what they desired, that makes these situations unequal.

Selecting <u>Against</u> or Selecting <u>For</u> Traits?

While the specific terminology, selecting *against* and selecting *for*, have been used several times throughout this composition, I would not be particularly surprised if, unless you are well-versed in designer baby ethical literature, you reached this point without taking note of the difference between these phrases. This one-word difference, while seemingly minute, results in a critical distinction that must be made in the statement: *more individuals are in favor of selection <u>against diseases</u> than of selection <u>for 'benign'</u> or superficial traits.* Though these two phrases both ultimately result in trait selection that 'betters' the genome -- one by removal of bad, one by addition of good -- the mechanism of decision-making has potential to be two different ethical scenarios. The former, *against diseases,* uses the elimination of traits to perfect what is desired, and the latter, *for benign traits*, choice selection. Ultimately, the ethical implications of genome editing technology are dictated by the use of one of these phrases and the morality of the actions that ensue.

The concept of selecting *against* particular traits undeniably has similar undertones to the eugenics movement of the 20th century. I believe that many are hesitant to support genetic engineering as, even though it is the 'nice' way of preventing certain groups of people from reproducing, it is still incredibly problematic. The goal of eugenics was to eliminate the members of society, through selective breeding, who reduced the quality of the gene pool of society; namely, criminals, those with mental illness, and the poor. The Nazis took this notion of eugenics to a new extreme when they began to exterminate the members of society who did not fit their criteria for reproductive worthiness. Recognizing that the fear of eugenics resurfacing is

likely to be a prevalent concern associated with editing the genome, Savulescu addresses this issue. He begins with the question of how exactly we decide which characteristics should be enhanced. There is nothing unintentional about the way in which he formulates this question, avoiding the concept of *eliminating* particular qualities.

Savulescu makes the distinction between the eugenics concept of weeding *out* the adverse traits, and the genetically-engineered *enhancement* of beneficial ones, very clear. The biggest distinction between the eugenics movement and modern eugenics practices, he states, is who they were ultimately for. While 20th century eugenics was implemented according to what the State felt would create 'a healthy population,' achieved through coercion, the goal of modern eugenics is for the good of the individual, rather than for society. He argues that the modern eugenics takes place today in the form of testing for various disorders. He continues that, it is also very common, in addition to "acceptable because it is voluntary, gives couples a choice over what kind of child to have, and enables them to have a child with the greatest opportunity for a good life." (Savulescu)

Societal Implications

It would be easy for the members of society who will not be utilizing this advancement to simply dismiss it as irrelevant and unworthy of their concern. Yet this ignorance is far from the truth and is what may allow this technology to overwhelm even those who supported its implementation. The socioeconomic effects will not only impact those who desire to use, yet cannot afford, this technology, but all members of society. Genetic engineering has the power to expand societal gaps to levels even beyond how they exist today. Just as with any cutting-edge technology, the price associated with genetic engineering is outlandish and, according to the director of the Massachusetts Institute of Technology's 'NEW Drug Development Paradigms',

Mark Trusheim, the solution is not in sight. Numerous companies attempting to broadcast their gene therapies, the predecessor of CRISPR in which pieces of genetic code are inserted into cells by viruses, have experienced great resistance due to their costs. uniQure created a gene therapy, Glybera, costing each patient $1.4 million dollars, and Spark Therapeutics created another for treating Leber congenital amaurosis 2, costing a half-million dollars, and that is only for one eye. This, as Dr. Siddhartha Mukherjee, oncologist and author of "Emperor of All Maladies," discussed in his speech at the American Society of Clinical Oncology meeting in June 2017, is what will worsen the divide between the elite few that can afford such medication and those who cannot. He verbalized a fear shared by many that these therapies, with costs of six or more figures, will raise the costs of treatment so that it will be affordable for fewer and fewer. Additionally, the lack of generic versions of CRISPR allow companies free reign on what to charge for these services. Such fears are heightened by the prospect that these treatments will likely not be covered by insurance, making them even less affordable. Insurance companies such as VantageBlue, Select Health, and VIVA Health, to name a few, have already declared that their policies do not cover gene therapy, which likely extends to CRISPR-based treatment (Kozubek, 2017).

It would follow that the members of society who can afford the treatment will become increasingly more attractive for jobs, while members of the lower and middle classes will have diminished chance to outcompete. This idea, naturally, would inspire feelings of unfairness for those who would automatically seem less qualified when viewed next to those who were able to receive treatment. Sandel, in his same composition mentioned above, seeks to silence this 'fairness' argument. He argues that "from the standpoint of fairness, enhanced genetic differences would be no worse than natural ones," under the assumption that they are available to

any individual and are safe for use. (Sandel) This technology is not changing the social concept that there are always certain athletes that are "better endowed genetically than others." (Sandel) If we had never argued the fairness of these individuals competing against others, he argues, why would we begin in this present scenario?

Through analysis of the greater implications of genome editing technology, it becomes evident that, as a society, we are at a crossroads; one at which we can continue to pursue this technology, or we can realize the dangers it poses, not only to our society, but more importantly, to the human dignity of the person. Genome editing, if we permit, has the ability to foster significant beneficial enhancements in particular realms. Yet, as mentioned throughout the discussions above, will we learn to demonstrate self-control in our utilization of this advancement, or will our human nature allow it, ultimately, to become a calamity?

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