Constraining Omnipotence: How CRISPR Must be Regulated in the Coming Age

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Genetic disorders cause about 50% of all childhood deaths in industrialized countries and 30% of all pediatric hospital admissions (WHO 1997). As such, recent advancements in gene therapy stand to benefit billions of humans across the globe. Clustered Regularly Interspaced Short Palindromic repeat DNA sequences (CRISPR-Cas9) is the latest iteration of strategic genome editing technology, allowing researchers to modify select portions of DNA sequences with direct influence over the "blueprint" of a cell. This capacity to permanently eradicate or insert specific traits can thus be utilized to eliminate hereditary and chronic diseases that previously had no cure (Tomlinson, 2018). Since these types of targeted genomic modifications would have otherwise taken millions of years to achieve naturally, CRISPR maintains the capacity to vastly accelerate the process of human evolution to unprecedented levels. However, little attention has been directed towards delineating a standardized regulatory protocol of the field. This paper will thus explore the implications of genetic engineering technology such as CRISPR to develop an ethically compliant regulatory framework for use within the United States.

Procreative Beneficence

Julian Savulescu, a prominent figure in the field of bioethics has designed a framework with which to evaluate procreative concerns. His principle of Procreative Beneficence (PB) adheres to a "common-sense" morality, where parents should always choose what they believe will create the best life for their children (Kahane, Savulescu, 2009, p. 274). He applies this principle to a host of contemporary procreative decisions, citing how parents with the choice of raising the same exact children under financial duress or as millionaires will always choose the latter in an effort to better support their children. In this regard, there is a financial incentive to

wealth as it can (but does not always guarantee to) provide children with a better life. Similarly, parents will always choose to raise children while they are emotionally stable rather than when they are under severe emotional duress (assuming all else equal), demonstrating the emotional incentive of mental wellbeing. Savulescu argues that there is a parallel moral incentive to raise children with the best chance of life via genetic engineering, and that this component is to be weighted equally against other procreative decisions. Henceforth PB recognizes the "genetic endowment" by parents to a child in a similar manner to their financial or emotional endowment while raising children, and procreative decisions require a delicate and contextual balance of these competing forces. He states that should a couple decide to have a child, they have "significant moral reason" to choose of the "possible" children, the one who would be most likely to experience the "greatest wellbeing", be the "most advantaged child", or otherwise have the "best chance" at life (ibid, p. 276). In the following sections, these core pillars of PB will be further analyzed before utilizing the framework to evaluate several relevant case studies to ultimately develop a comprehensive picture as to how genetic engineering technologies such as CRISPR must be moderated in the future.

In labeling PB as a "moral reason" rather than an absolute obligation, Savulescu succeeds in making this principle compatible with the natural decision-making of parents. When possible, few would argue that couples should not wait to be financially or emotionally stable enough to support a child in order to give them a better chance of life within the couple's means. PB is simply an extension of this natural philosophy, highlighting how while couples should not be forced in choosing to have children with the best possible chance of wellbeing, there is a significant reason to do so utilizing whatever tools are available. In a PB framework, CRISPR simply represents a new tool available to parents who wish to be able to support their children

beyond emotional, financial, and personal means. Since many already fundamentally adhere to such a principle, applying PB to genetic engineering does not inherently deviate from the current social standard. Furthermore, the emphasis on selecting the "most advantaged" child lends it flexibility as its understanding of wellbeing is entirely contextual. While there exist several equally valid definitions of what constitutes a better or best life, Savulescu is neutral in this debate. PB's understating of wellbeing is "plural" and "open-ended". In this regard, it does not specifically delineate any particular understanding of wellbeing, but rather asks parents to apply their own definition. PB's relegation of responsibility to the perception of the parent is thus compatible with any situation, and its understanding of the contextual divergence of wellbeing prevents it from being constrained by normative, social, or genetic denotations of the term.

Contextual considerations are further developed in PB's understanding of disability, which Savulescu writes is critical in the aforementioned determination of wellbeing. Whereas many ethicists use either a biologically normative definition of disability or a purely socially constructed definition of the term, PB highlights the shortcomings of each. Savulescu explains how erectile dysfunction, for example, is considered a disability by most if not all members of society. However, according to normative inquiry, such deficiency is to be expected and does not deviate from the species norm (males are genetically designed to lose function with age). Henceforth, normative inquiries fail to recognize disabilities that may be inherent to species. Similarly, while a purely socially constructed term of disability is useful in capturing the notion of social prejudice limiting an individual's wellbeing (and thus also highlights the contextual nature of disability as it is contingent on a given society's values), it also is not always applicable. Indeed, Savulescu highlights that in some contexts, having perfect health can be a disadvantage, such as in Russia in the 1800s, where men of good health meant 15 years' service

in the army, with a significant chance of being killed (ibid). Deafness, for example, would be incredibly useful in a world of constant, cacophonous noise. These are prime examples of socially constructed disabilities that only exist within the confines of their particular contexts. However, such social constructions are not always adequate in capturing the inherent disabilities in life. Few would argue that there is any benefit to debilitating joint pain regardless of any social context. Savulescu labels this as an "instrumental badness" that can be described to some extent via a biological normative inquiry but can be completely overlooked with a constructionist theory. Moreover, although a constructionist theory lends itself to recognizing contextual markers, it still only does so from a broader social context with consideration for personal disabilities. In current times color blindness is hardly seen as a disability given that technology has advanced to the state where those afflicted can still live functional and fulfilling lives. It is at most a mild disability if even to be considered one at all. Henceforth, the relevant social forces prevent color blindness from being a debilitating disability for society as a whole. However, should a master painter suddenly fall colorblind, many would agree it to be incredibly debilitating for that individual. Neither a biological normative nor socially constructed definition would accurately depict such an event. As such, PB utilizes a hybrid of the two, recognizing some of the biological qualities that transcend social norms while simultaneously recognizing the contextual forces, both socially and personally, that contribute to an understanding of disability

Ultimately, PB is a useful framework with which to handle the complex questions surrounding the regulation of genetic engineering as its delegation as a moral reason allows us to better balance the competing forces that may exist when raising children. Moreover, its commitment to only altering possible children restrains the limits of the technology enough such that it can be digested from a regulatory standpoint (making laws around technology is much

easier when the bounds of the technology have been clearly defined). Additionally, its understanding of wellbeing and disability as a combination of socially constructed forces, inherent biological forces, and context and person-dependent forces lends it flexibility in mediating the more subjective factors that regulate procreative decisions as is currently seen now with child-related legislation. PB will thus offer a foundational moral framework to investigate how CRISPR should be regulated in the age of genome editing.

CRISPR Overview

CRISPR-Cas9 is a system that allows for the targeted editing of DNA *in vitro*. CRISPR itself is a naturally occurring molecule found in bacteria but is often used as a catchall term for systems that enable researchers to program the CRISPR molecule to make precise cuts along a cell's genome (Broad Institute 2020). The system is facilitated via a guide RNA (gRNA) molecule which identifies particular portions of the DNA strand to initiate precise cleavage by binding to the targeted DNA through base complementarity (Jinek et. al, 2013). This base-pairing thus allows for the insertion, deletion, suppression, or activation of an entire genomic sequence driven by non-homologous end-joining pathways, homology-directed repair pathways and catalytical insertion of transcriptor activator/repressor fused Cas9 respectively (La Russa and Qi, 2015). To this end, CRISPR gives scientists unprecedented control over germline gene expression presenting the opportunity the permanently modify previously heritable sequences. For example, rather than shaving down a mustache and waiting for the hair to invariably return, scientists can now eliminate hair follicles at the root, such that they never come back. Moreover, due to the nature of the technology, the hair follicles will also never exist in one's future

offspring, completely erasing the ever-present mustache dilemma.[1] However, such modification is contingent upon a successful gRNA molecule that can maximize on-target activity (guide efficiency) while also minimizing potential off-target effects (guide specificity) (Wilson and Bauer, 2018). Balancing these two requirements can be a "combinatorial challenging task" and as a result, significant efforts in recent years have been focused on developing computational tools to assist in the design of gRNAs so that the best target sites are selected while avoiding undesirable targets based on predicted low efficiency or a high potential for off-target effects (ibid). Such advancements ultimately improve the CRISPR system such that it can be safely implemented in the clinical setting.

Case Context

Sharon Duchesneau and Candy McCullough elected to have a deaf-born child by utilizing sperm from a dead sperm donor. Like many others within the deaf community, Duchesneau and McCullough did not see deafness as a disability. Rather, they see being deaf as defining their cultural identity and signing as a sophisticated, unique form of communication (Savulescu, 2002). This particular case will be analyzed to construct a model with which to evaluate the ethics of genetic engineering. Information regarding the case was taken from various scientific journals and news outlets to construct a comprehensive understanding of the as well as compile all competing factors relevant to their decision. The case will be evaluated utilizing the aforementioned PB framework.

[1] This example is slightly misleading as many gene therapy treatments do indeed stop the mustache from ever growing, but have no effect on the mustaches of future generations. CRISPR, by contrast, eliminates the mustache for the individual and all of their children for eternity. This difference is known as somatic vs. germline editing, where somatic editing permanently affects the individual, while germline editing affects the individual ***and*** all of their future offspring (NIH, 2017). Currently, CRISPR is the only method of targeted germline editing with high specificity.

Research Question

This paper will explore the competing forces that influence procreative morality to answer the question of how germline genetic engineering techniques such as CRISPR should be modulated to ensure ethical outcomes. It will do so by challenging normative understandings of social and genetic wellbeing in addition to disability as a combination of socially constructed forces. This analysis will be performed in accordance with a PB framework of the aforementioned case of Sharon Duschneau and Candy McCullough. I will identify the given disability and its contribution to the subject's wellbeing, weigh it against other identifiable procreative decisions (financial/ emotional status), determine the morality of the choice against a PB backdrop, and extrapolate that determination to include the germline considerations. The resultant model will then serve as the first comprehensive and practical regulatory guideline for ethical implementation of germline editing techniques such as CRISPR.

Methods

Research was conducted through a case study of somatic genetic engineering to develop a model with which to ethically balance the notions of wellbeing and disability. This was accomplished by ascertaining the morality of utilizing genetic modification to promote or remove a disability via its impact on wellbeing as described in the PB framework. Since PB posits that wellbeing is the ultimate determining factor in ethical procreative decision-making, modifications that served to promote wellbeing were considered ethical while decisions that inhibited wellbeing were considered unethical. This general model was then be applied to consider the consequences on future generations to capture the dimension of hereditarianism within germline modification. A similar analysis was performed, where decisions that restricted the wellbeing of future generations were considered unethical whereas decisions that did not

restrict wellbeing of future generations were considered ethical. Disability was understood as any condition that inhibits the intended physiological function of the human body. Such a definition was chosen as it captures the benefit of a normative inquiry, allowing for comparison against a general standard while also considering the evolution of an individual's biology over time (preventing the aforementioned erectile dysfunction dilemma from occurring). Moreover, it is broad enough to be compatible with the social dimensions of disability. In this regard, I did not aim to exhaustively and precisely define what all disability looks like, but rather put forth an understanding of the term that is contingent upon a biologically quantifiable threshold.

Results

Sharon Duschneau and Candy McCullough's use of gene-editing technology to give birth to a deaf baby was found to be ethically compliant within a PB framework. Since there existed no discernable financial, emotional, or otherwise personal factors immediately present, the determination of wellbeing was solely dictated by the disabled status. Henceforth, although deafness is considered a disability given our definition, the particular social circumstances of the family (two deaf parents) overrode this distinction as it could be reasonably argued that a lack of deafness would result in more harm to the child given the home environment. As such, the parents were acting within reason to promote the wellbeing of their child. This decision remains ethically compliant with a PB framework for germline editing as it does not necessarily infringe on the future parenting rights of the child; raising a deaf child does not guarantee that the child themself will be forced into having deaf offspring. In this regard, the decision of Duschneau and McCullough was not deterministic for the future parenting rights of the child. Extrapolating this into a more generally applicable model, parents only have the right to genetically modify if it is to 1) prevent net disability and 2) promote a nondeterministic condition.

Case Analysis

As mentioned, the lack of extraneous factors (financial/emotional status) in raising the child result in the disabled status of the child being the only determinant of wellbeing. As such, there existed only 4 possible outcomes of such somatic engineering under a PB framework (Figure 2).

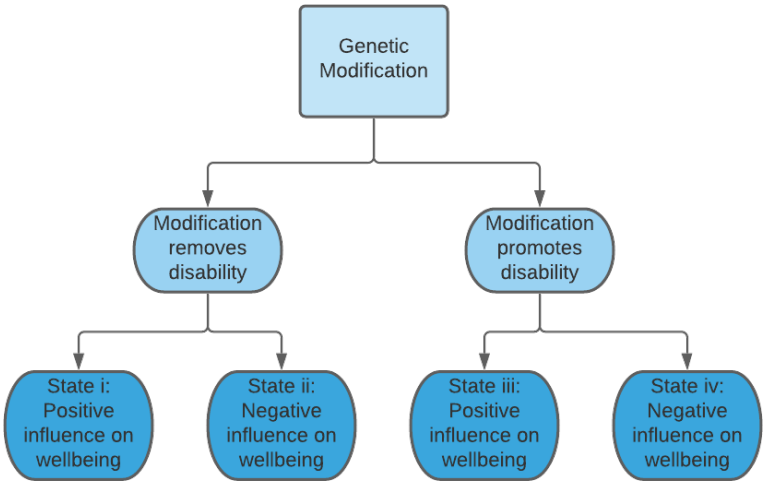

Figure 2: Flowchart of all possible outcomes of somatic genetic engineering within a PB framework.

State I represents the condition wherein genetic modification would remove a verifiable disability and positively contribute to the perceived wellbeing of the child. This is **always** ethical under a PB framework as any physiological impairments have been removed, and doing so does not present any socially constructed disabilities that would otherwise hinder wellbeing. Such an example would be utilizing genetic modification to prevent a rare cardiovascular disorder that would otherwise severely impair if not outright kill the child.

State II represents the condition wherein genetic modification to remove a physiologically defined disability negatively impacts the perceived wellbeing of a child. This will **never** be ethical under a PB framework as the parent is thus subjecting the child to a less advantaged life, violating the core tenants of PB. In other words, since disability is partially socially constructed, the removal of a physiological impairment that results in a "larger" social impairment would actually expose the child to a larger "net" impairment. Such an example would be in the contemporary movie BirdBox, where individuals with functioning eyesight were systematically hunted and killed. According to our definition, blindness would still be considered a disability as it impairs the intended function of the body. However, the lack of eyesight results in a statistically higher chance of life. Henceforth, the choice to remove a biological disability would be unethical as it would adversely impact the probability of living a successful life due to extenuating social influences.

State III represents the condition where modification is utilized to promote a disability with a positive outcome on wellbeing. Similar to State II, if it can be reasonably demonstrated that the child stands to live a better, more advantaged life as a result of a physiologically defined disability, then it is ethical to do so. In this regard, the removal of a social impairment mitigates the presence of physiological impairment. Such an example would be the case in question of Duschneau and McCullough, where promoting the physiological disability reduced impairment in their immediate social environment. In their case, it can be reasonably argued that the parents are much better suited in bringing to life a deaf child that identifies in part with their disability. Moreover, it can be reasonably argued that bringing into a child that is *not* hearing impaired, would be a much larger detriment to the child's wellbeing given the parents' lack of experience in raising such a child. Indeed, having the propensity to learn multiple languages is commonly

considered a positive outcome as it enriches the vernacular of an individual (Monroe, Andrade, 2018). However, many hearing children of deaf parents are then forced to become "language brokers" of families, bearing the responsibility of handling all family communications. Naturally, such unwanted pressures can serve to significantly burden children, as they are thus exposed to sensitive and potentially information by necessity (ibid). As a result, many children find themselves in a situation known as 'role reversal', where a child feels responsible for the parents and the parents expect the child to be responsible for them (Buchino, 1993). Moreover, Morales and Hanson (2005) assert that children who served as such language brokers are exposed to the additional stress of attempting to protect their parents from negative comments or embarrassment while interpreting. In this regard, having the capacity to hear can in many ways impart tremendous amounts of responsibility and psychological stress onto a child that would otherwise not exist if they were deaf. The constant role of a mediator can also serve to alienate children from either world, taking from them a sense of parental comfort. Consequently, a very strong argument can be made that resolving this particular disability opens the door to a plethora of other psychological stresses, which can serve to impair the wellbeing of the child more so than simply being deaf. As a result, inducing disability in the pursuit of wellbeing is not necessarily unethical, and in the specific case of Duschneau and McCullough I would argue that it was an ethical conclusion given the extenuating circumstances.

State IV represents the conditions where modification is utilized to promote a disability with a negative influence on wellbeing. Such an example would be intentionally inducing a rapidly growing, terminal brain tumor into offspring. In this case, the offspring will always lead a less advantaged life as a result of intervention. As a result, since PB values wellbeing above all else, this choice will **never** be ethical regardless of social considerations.

Germline Considerations

With a framework with which to evaluate somatic modification established, we must now consider the germline dimensions of emerging gene-editing techniques such as CRISPR. In order to extrapolate the results of this case to a germline model, we must also extrapolate our understanding of wellbeing further into the future. Implicit in the aforementioned understanding of wellbeing is that parents are *qualified* to make those subjective, contextual decisions regarding their child. This notion is complicated when the decision in question permanently affects the entire lineage as opposed to just a single child as it is much more difficult to come to an educated conclusion regarding an event the further away it is. Consequently, although the definition of wellbeing will not change, germline decisions must consider the additional complication in accurately forecasting wellbeing for future generations. We can thus modify the original distribution of possible choices to only include the potentially ethical options (States I & III) as well as add deterministic considerations for each (Figure 3).

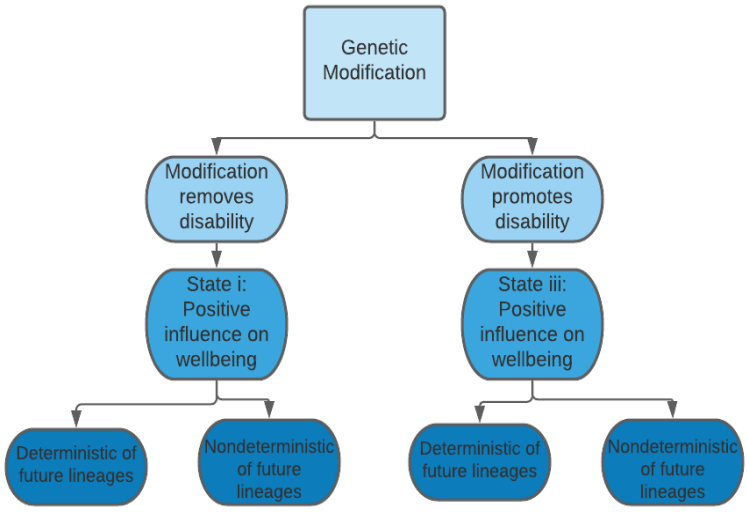

Figure 3: Flowchart of all potentially ethical outcomes from germline modification

In examining this new germline distribution, the only areas of interest are modifications that result in deterministic outcomes (nondeterministic outcomes are essentially equivalent to somatic modification, which has already been discussed).

Deterministic modifications from State I are instances where the prevention of disease is forced upon further lineages. It stands to reason that such a decision would in fact hold for future generations. If wellbeing is only inhibited by deviation from intended biological function, then such will hold in the future unless the standard of intended function changes. Following this logic, if the standard changes such that the disability deviates more, then a deterministic modification still holds as ethical. Conversely, if the standard changes such that the disability becomes the norm, there no longer exists a need for genetic modification. For example, preventing a rare hereditary cardiovascular disease will always be in the best interest of the child if the disease is the only thing impacting wellbeing and contracting the disease deviates from biological norms (hence deterministic decisions are ethical). Should human biology change such that the condition becomes even further from the norm, genetic intervention will still be supported. Should human biology change such that the condition becomes the new biological standard, no modification would be required to rectify the former disability. As a result, deterministic choices from State I will always be ethical.

Deterministic modifications from State III are instances where disability is induced for the benefit of the child that is also forced upon further lineages. Such a decision promotes some sort of deviation from physiologically intended standards in the pursuit of providing a better life for the child. As a result, these states arise from external, socially constructed impairments to wellbeing that are greater than and in opposition to a given biological disability (such as in the Duschneau-McCullough case, where the external factors of raising a hearing child posed a

greater threat to wellbeing than raising a deaf child). This case differs from State I in that there do exist pathways wherein the relationship between disability and wellbeing could change. The social circumstances that make promoting disability viable for a given couple may not exist in future generations, and thus to decide for those generations amidst such uncertainty would be unethical. For example, imagine a couple with achondroplasia (dwarfism) decide to have a child like them as their circumstances justify bringing to life such a child. While that might be an ethical decision to make for the parents as it would put them in the best position to raise a child similar to the Duschneau-McCullough case, it may not be the case for the child and their future partner. The child may decide to procreate with someone who does not have achondroplasia, and as such the social circumstances that define the new couple's relationship are completely different from the original parents. However, since achondroplasia is a dominant trait, the new couple will *have* to give birth to a baby with achondroplasia (assuming they opt for a "natural" birth). In this regard, the decision of the original parents forces a particular lifestyle onto future generations. The difference between State I and State III is that in State I the circumstances of the disability are genetically fixed and unvarying. It is known that the disability will always exist as it was first seen, and the decision to change it in the future will be influenced by exactly the same factors as the present (hence future generations would come to the same conclusion as the present). By contrast, in State III, the circumstances of the disability can very easily change, making it impossible to accurately forecast wellbeing. The Duschneau-McCullough case, for example, is nondeterministic as it does not force the child into the same situation as the parents (future generations are not forced into procreating with a deaf partner nor does the presence of one deaf partner necessitate a deaf child). As such, deterministic modification that promotes disability is unethical under a PB framework. This leaves us with a working model to evaluate

the ethics of germline modification: modification to remove a disability that will have a positive influence on wellbeing is ethical regardless of future considerations while modification to promote a disability is only ethical when it is nondeterministic for future lineages. (Figure 4).

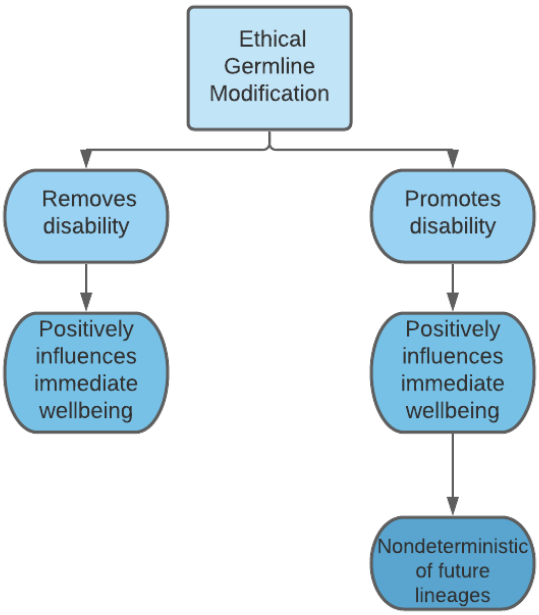

Figure 4: Flowchart of requirements for ethical use of genetic engineering

Discussion

This paper proposes a working model with which to evaluate the ethics of emerging germline modification technologies. Since previous discussions of the topic have focused on the need for such frameworks without proposing any in their own right, this work is significant as it is the first to delineate specific and widely applicable infrastructure to be utilized for regulatory purposes. As such, this model has a practical use case as an ethical guide for regulatory agencies such as the FDA. It is important that such guidelines continue to be published and revised given the gravity of germline engineering technologies. CRISPR is by all accounts the single most

influential tool to our species that has ever been observed because it possesses the capacity to alter what we are as organisms. Every single advancement in human history thus far has only been relevant in how we organize within society. Whether through efficiency (industrial machines, electricity etc.), dissemination of information (printing press), or even fear (nuclear weapons), each major accomplishment in human history is significant because it enables or restricts a *human* practice. CRISPR, however, penetrates one level deeper, challenging what we even are as humans. There has never existed anything with such direct control over what we are as a species. Henceforth, as scientists rapidly approach clinically feasible applications of the technology, it becomes crucial that proper regulatory constraints are preemptively enforced and a general ethical consensus is reached within the bioethics community, and this paper is the first iteration in doing so.

Caveats

The largest limitation of this investigation is that it is relatively agnostic to purely socially constructed disabilities. The choice to define disability as having a social component but also constrained to deviations from intended physiological function was necessary because otherwise an argument could have been made that anything is a disability. For example, one could argue that being 6 feet tall is a disability because their crush's minimum height threshold is 6'2" for a romantic partner. Intuitively, we understand such to not be a disability comparable to being blind or deaf, but without some sort of reliance on deviation from intended biological function, such an argument is valid (being 6 feet tall does not substantially inhibit intended biological function to be considered a disability in the model presented in this paper). However, the consequence in doing so is that the model is also incapable of dealing with more nuanced inputs. For example, it has been well documented that particular racial groups within society are disproportionately and

systemically disadvantaged. They are statistically exposed to more harm relative to other groups, and although race is purely a social construct, it does have an identifiable biological tie that CRISPR could feasibly eradicate. Similar arguments can be made on the basis of sex, with particular sexes being disproportionately exposed to many different sources of violence, financial inequities, and discrimination than others. As such, an argument can be made that these conditions constitute a disability within (and constrained to) the current social system. However, these conditions would not be recognized as disabilities in this paper since they do not inhibit intended function (and thus not considered for modification). While I do not intend to answer the question of whether race or sex is a disability in America, I would like to point out that the model that has been developed in this paper is ill-equipped to handle such a discussion. One subsequent flaw of this paper is that it determines a relatively narrow scope of what can be considered for modification and is thus limited in its capacity to tackle more complex problems.

Future Work

Future work of this investigation would involve more comprehensive considerations for purely socially constructed disabilities as described in the previous section. A future model would be sophisticated enough to filter the "non-valid" examples (such as wanting to be 2" taller to impress a crush) but having the capacity to deal with more difficult questions such as race and sex as a disability and whether modification of those characteristics would be ethical. As such, future work would delve into the ethics of consensual eugenics, where individuals actively choose to modify their gene pool in pursuit of a particular phenotype. In doing so, it would explore the impact of larger systems of oppression on the supposedly independent and consensual decision. This model could then similarly function as a regulatory framework for the

FDA and bioethics community at large but would have the added benefit of being slightly more refined than the model proposed in this paper and capable of more nuanced inputs.

Impact

As an engineer, this paper has demonstrated to me the vast complexity in modulating technology for ethical uses in society. Moreover, CRISPR in particular has highlighted how directly current choices can impact future generations. As such, unethical decisions do not just affect us here and now, but are further propagated down lineages, indicating the compounding effects of unethical decisions and inequality for particular segments of society. This has thus taught me that we must be just as cautious of the future impact of any technology and its lasting effects on society as we are to its current implications as we work as engineers.

Conclusion

This work has developed a comprehensive model with which to regulate germline modification. In doing so it highlights the complexity of mediating both the social and biological factors that determine wellbeing and the difficulties in relying on (and omitting) normative understandings of the term. Moreover, it demonstrates how procreative decisions are becoming more explicitly influenced by the deterministic consequences for future generations. In this regard, CRISPR will spark a fundamental shift in the ways in which individuals make decisions. Many families will be forced to consider the consequences on future generations, a mindset that has been largely abandoned in many modern societies. With the advent of "instant gratification technologies" that are always vying for the time and attention of users via notifications, pop-ups, blinking messages and other devices to monetize and ultimately optimize immediate user engagement, CRISPR will force individuals to take a step back and think more of future

consequences than present desires. Henceforth, CRISPR is significant not only as a scientific advancement, but moreover in the way in which it will mold future community interactions to live their life. This paper therefore offers a working model to initiate such conversion within the bioethics community that can also function as a preliminary regulatory framework for large governing agencies like the FDA that have as of yet refrained from presenting a working model.

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