ENGR 0711 Budny, M&W 4-5:50pm
L06

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BIOENGINEERING: CRISPR ETHICS

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GENETIC ENGINEERING: A NEW FRONTIER

The discipline of genetic engineering began in the 1970's when 2 scientists, Herbert Boyer and Stanley Cohen, successfully modified the genes of a live bacteria. Ever since, the field has developed at an incredible pace, working its way through more complex organisms and developing more complex methods. In just 4 short decades, genetic engineering has already realized such feats as cloning, in vitro fertilization, and genome editing.

CRISPR, genetic engineering's newest invention, is a new tool that enables high precision genome editing. CRISPR stands for "clustered regularly interspaced short palindromic repeats", and Cas9 stands for "CRISPR-associated nuclease 9." Together, CRISPR-Cas9 refers to a new technology in gene therapy whereby bodies are made to mimic bacteria. For bacteria to fight off viral infections, they employ what is now called the CRISPR system. This self-defense mechanism is like a human's antibody response, except it goes one step further. After the virus is neutralized, bits of the viral DNA are spliced by Cas9 directly into the bacteria's genome, creating a genetic vaccination. Misreads of the added information are prevented by caps of the actual clustered repeats, which serve as markers and directions on how to execute the new gene. The significance lies mostly in the Cas9 protein. With it, extremely precise, double-stranded cuts can be made anywhere in the Human DNA sequence. Accuracy and precision are provided by an accompanying 20 base string of RNA that lines Cas9 up with the desired cut site. Such cuts prompt the body's own natural response to mend the break by either reattaching the ends or filling the hole with another sequence of DNA.

Many hail CRISPR as a sort of panacea because of its ability to cure congenital disease, but with clever application, it can also be used for germline editing, live genetic enhancement, ecology alteration, and so much more. With the possibility to alter the genes that control our very behavior, the implications of CRISPR are quite literally endless. However, although CRISPR seems like the ultimate solution, such a powerful tool prompts much caution and deliberation before use.

NEW SOLUTIONS, NEW PROBLEMS

CRISPR enables us to open many new doors in the world of science. These doors can certainly lead to many good things, but they should always be scrutinized for any flipsides or unintended consequences that may arise. The entire field of biological engineering is shrouded in bioethical concerns, and CRISPR itself is a high point of contention. For instance, CRISPR may be used to alter the human germline. This means that edited genes can be passed down to future generations – is this ethical? Does it violate the rights of the children? If it were a congenital disease going to be cured, to what extent is consent needed? Another scenario is genetic enhancement – how would athletes compete with one another? Would a separate league be created or would they be entirely banned – what sort of genetic modification would be permitted? Aside from human modification, CRISPR could easily be used to alter ecology and nature. Though native species could be restored, any carelessness might result in entire ecosystems being destroyed. What sort of ethical code should be implemented? Along with the endless possibilities of CRISPR come an endless amount of careful consideration that needs to be straightened out before implementation.

PRECEDENTS AND PRINCIPLES

Though these may seem like far off hypothetical questions to address, they are closer than we think. Biomedical technology is moving at such a rapid pace that the dreams of yesterday are quickly becoming the realities of today. Answering these questions may seem difficult, but there already exists a code of ethics to help find the morally correct decision. This paired with several precedents form a clearer picture of how to deal with the ethical concerns of CRISPR sure to come in the near future.

The National Society of Professional Engineers (NSPE) has a strict code of ethics that outlines the

morally acceptable behavior for an engineer in any morally compromising situation [1]. A highly condensed version of the code is that an engineer should always act in the best of interest of the public and his/her clients, openly without any sort of deception. Though this does not apply directly to the use of CRISPR as a technology, the same principles of beneficence and honesty can be applied universally. "Beneficence," as defined by Stanford University Researcher Tom Beauchamp, is "the moral obligation to act for the others' benefit" [2]. Especially as an engineer, one holds full responsibility for his clients – just like any other profession, engineers must represent the interests of their clients, which tend to be their own physical well-being. Honesty implies more than simply telling the truth when asked – it requires fully transparent operations and even the active informing clients and proper authorities of anything that may be of any significance. This sort of full disclosure ties in with the principle of beneficence, because information sharing is integral to the relation between client and engineer. There needs to be a bond of trust between the two so that they can cooperate to make the best decision for all parties.

The Biomedical Engineering Code of Ethics instead highlights the importance of confidentiality and overarching goals [3]. Keeping confidentiality between patient and engineer, as stated above, is necessary to respect the privacy and trust of the patient. Overarching goals here refers to beneficence on a larger scale – how work might impact not just individuals, but also the medical and social systems as a whole. The idea is to imagine how advancements in technology might impact the big picture. Thus, when combined with the NSPE ethics, the two codes form a substantive guide for approaching dilemmas in ethics. The NSPE tells how one should treat the patient, the Biomedical Engineering Code focusses on the large picture, and both emphasize a healthy relation between client and engineer. These codes can be used in conjunction to analyze past events, which can in turn be used as precedents when determining the future.

Because genetic engineering is so new, CRISPR especially, there are very few precedents to discuss. For nearly a decade, CRISPR undergone extensive testing in animal trials. In 2015, researchers (Ye et al.) conducted experiments on 120 mice with malformed CNGB3 genes [4]. The gene was then corrected and showed uniform adjustment and correction, strongly suggesting that CRISPR is a safe tool. An early 2016 study (Liu et al.) performed a similar experiment in which they varied the dosage. [5]. Varying the level of dosage, they concluded that though high dosage has higher efficacy rate, it also has a much higher risk of rejection associated with it. This conclusion again brought CRISPR's safety into question and stalled whether or not it should be tested on humans – researchers and ethicists wanted to know for sure if it were in a patient's best interest to undergo risky testing, and what level of risk it was in order to better inform potential patients.

However, the first wave of human trials have just begun to get the green light, and scientists so far are working on curing some of the most prevalent problems. This past winter, Chinese scientists began trying to genetically modify human embryos to be resistant to HIV [6]. While results are not in yet, this is a massive step for the entire field of medicine. Rather than fixing a mutation after it occurs, this method rather alters humans to not develop the problem in the first place. As mentioned earlier, yesterday's dream is fast becoming today's reality, and so discussion is necessary before moving much further. Applying the principles of NSPE and BMES Ethics Codes, we can see that, not speaking about the nature of altering human life itself, in practice, the work done was ethically sound. According to the article, the embryos were donated to science for the purpose of research. All necessary approvals were received, and the entire experiment is open to the public. Setting such a carefully watched and set up precedent is beneficent to the acceptance of gene therapy and to those who may suffer from AIDS in the future. The project has a wholly humanitarian goal of helping to prevent AIDS in the future, and thus attempts to act on the best interests of humanity. It is certainly fortunate the first human trials started off on the right foot, but for a possible negative consequence of genetic engineering, we need look no further than the 1997 sci-fi movie *Gattaca*.

Gattaca is a sci-fi romance that explores a possible outcome of widespread gene editing [7]. In the movie, gene editing is such a widely practiced operation that in that era, the majority of humans are genetically modified to be optimized. As a result, society suffers no longer from racial or economic discrimination, but rather from genetic discrimination – based on the quality of one's genes. Applying NSPE and BMES codes, there is a clear violation of beneficence. The gene editing technology is no longer helping all of humanity, but rather has created a rift between the genetically modified "elites" and non-genetically modified "commoners." In the movie, there also is no confidentiality, as your genetic makeup serves as your ID. This fictional system that genetic engineering has created can be easily judged to be unethical based from its total breach of confidentiality and failed beneficence, which not only harms some individuals and but has also pushed society as a whole in the wrong direction.

Using these two precedents, both fiction and nonfiction, what then can we say about the implications of CRISPR mentioned before? Can we answer the question posed or determine the best course of action?

CRISPR CASE BY CASE

First is altering the human germline: is it ethical to alter a child's genes? This may be accomplished several ways – either by altering a parent's germline or by altering the genes of the embryo itself. CRISPR can cure malformed genes and hence congenital disease, but CRISPR enables more than correction of mutated genes. Because it is such a powerful editing tool, CRISPR allows for the creation of "designer babies." According to *The Embryo Project*, a designer baby is "a baby genetically engineered for specially selected traits" [8]. These traits can range from resistance to a particular disease to hair and eye color. Once gene expression is controlled, you can truly an embryo to grow into nearly whatever you would like. This notion certainly has its proponents and doomsayers, but many of these judgements are made after initial impressions and have little basis in ethical thinking. Let us apply the NSPE and BMES Codes of Ethics to a scenario. Suppose a couple conceive a child, but after prenatal screening they find that the baby has Taysach's, a deadly congenital disease that causes a build of lipids [9]. Without a gene correction, the baby has a near 100% chance of dying by age 5. If I were the counselling genetic engineer, I would certainly advise them to get the operation. However, if the couple requests that I also have the gender of the baby changed along with its several other traits, this is a much greyer area. To remain honest, I would talk through the entire situation with them, however, I would not allow them to alter the baby in any manner other than fixing the Taysach's. This is because while it is in accordance with beneficence toward the couple and baby to save the baby's life, it is not in the baby's best interest to change – simply the parent's personal desire and preference. This is an extremely subtle point, but I am confident that this is the right path. Otherwise, a situation similar to *Gattaca* may arise, which was just determined to be an unethical outcome of gene editing.

Scenario 2 is similar to Scenario 1, except rather than modifying an embryo, the patient is a legal adult seeking physical enhancement. This is possible due to CRISPR's ability to affect both mitotic and non-mitotic cells. Although it would take much longer, essentially the same modifications would be possible as those of an embryo. However, this would be a direct alteration of an existing identity, which is the ethical dilemma. If I were genetic counsellor to a man wishing to change the color of his skin, I would not approve, because I believe that it is merely his desire, not his objective long term best interest, to change. Another reason is that it is ethically better to use CRISPR conservatively than to use it boldly without reservation. This will ensure that each situation is understood to minimize damage done through careless actions. However, if he were instead trying to just cure an existing disease, such as, anemia, then I would be willing, as it is in his best interest to bring his quality of life up to standard – repair his identity rather than get a new one. In the context of sports, genetic modification may be thought of as a permanent steroid. I do not believe that it would be ethically sound for those with physical enhancement to compete with natural athletes. This is because the aim of competition is to find a difference in degree, but the introduction of enhancements, genetic or medicinal, introduces a difference in kind. This would make the two incomparable and therefore the two should have separate leagues. The final reason why I do not believe that physical enhancement is ethically correct is because this would lead to heavy commercialization – a shift away from medicinal use. In terms of ethics, this represents a departure from true beneficence to pure desire. Here, the NSPE's code and emphasis on whether it might truly be good for the individual patient would dictate a thorough examination of whether it would be truly beneficial.

HOW AND WHEN TO USE CRISPR

CRISPR is without a doubt a powerful tool, but as the adage goes, "with great power comes great responsibility." CRISPR is so fully charged with potential that one must be careful and fully aware of the consequences every step of the way. It is not something that depends on the circumstances, but rather the technology itself is in question. After reading the NPSE and BMES Codes of Ethics, it is clear that careful deliberation must be taken before every individual use of CRISPR. According to the each code, the principle of beneficence and honesty must be thoroughly followed. Honesty includes respecting your patient's privacy, and an important distinction must be made between true good for a patient and their simple desire. As a rule, I would only use CRISPR in further research and as a cure for those diseases that we cannot yet cure otherwise, taking each individual's circumstances into account every operation. CRISPR is still a new technology, so it is best to proceed with caution, but proceed nonetheless.

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ACKNOWLEDGMENTS

First, I would like to thank my friend and peer Audrey for staying up into the late hours of the night working on the paper and listening to music. I can honestly say that I probably would not have finished were it not for your company. Next, Sid Iyer and Jonathan Perlman woke me up when I fell asleep and or that I am eternally grateful. This assignment's completion hinged on that kind deed.

ADDENDUM

I really meant to clarify this before with either Ms. Newborg or Ms. Zellmann, but I never had the chance due to heavy testing in the week before the paper was due. So I suppose here I am writing this little note: No doubt my paper is formatted a little differently than other. Whereas others made up a scenario upon which ethics were circumstance based, I felt as if that would not work for what I was doing. CRISPR as a technology itself is an ethical debate, so I felt as if it were a different type of ethics that I was writing about than whether imaginary me should choose to inform my imaginary supervisor of some mishap or not. I attempted to still stitch it together, the bigger picture of ethics while still following this assignment's guidelines, but I felt that it did not match up nicely and comes across as sort of awkward. Anyways, I just wanted to let you know that I tried my best to bring two different things together and it certainly did not work out as well as I thought. I could have used another week with this assignment! Happy Thanksgiving!