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Submission for Nuffield Council on Bioethics Open Call for Evidence:

Perspectives on the Ethics of Genome Modification using CRISPR-Cas 9

For thousands of years, farmers have used selective mating and breeding to create desirable lines of crops and livestock harboring specific genetic traits. Scientists have used molecular biology techniques to modify the genomes of model organisms such as mice, yeast, and zebrafish for decades. But the new CRISPR-Cas 9 technology, initially recognized by scientists for its potential for gene editing in 2012, is by all accounts ushering a new era in genetics given the ease with which it can be used and the breadth of changes that can be made. [1-3] Combining this new method of gene editing with the tremendous advances that have recently made whole genome and whole exome DNA sequencing accessible and affordable, scientists now have unprecedented power to make targeted changes in genomes from many different species. [1, 3]

Indeed, making heritable genetic alterations to human embryos is now well within the realm of possibility: a Chinese group published results of experiments attempting specific genetic edits in non-viable (triponuclear) human embryos in April 2015.[4] Although their results showed that editing efficiency and off-target effects are problematic and must be improved [4], the work received much attention and generated significant controversy for its ethical implications. [3] Prominent scientists from around the world, led by David Baltimore, recently called for a moratorium on human germline editing so that technical and ethical concerns can be debated and addressed. [5] But perhaps not surprisingly, not everyone agrees a complete ban is the right step, including scientists who played major roles in developing the CRISPR-Cas9 technology: George Church believes a ban might have the unintended and undesirable effect of pushing germline editing research underground. [6] Jennifer Doudna advocates for caution regarding germline editing but warns a complete ban might be impractical given the widespread accessibility of CRISPR technology. [7]

The Nuffield Council on Bioethics has released an "Open Call for Evidence" asking for submissions of "information, insight and opinion" to aid its investigation into "whether genome editing itself raises any distinctively new moral questions or simply casts familiar questions in a new light." [8] This essay will reflect on two specific questions raised in the Open Call for Evidence: 1) what conventional moral principles does genome editing challenge? and 2) what are the issues of greatest moral concern raised by genome editing? [8]

To put the CRISPR gene editing technology into context, it is useful to consider how it differs from previous methods used by molecular biologists to edit genes. Simply put, the technology is quick, easy to use, adaptable, and low cost. [1-3, 9] Using CRISPR, scientific experiments that used to take years can now be completed over the course of a few days. [10] Jennifer Doudna told *Science News* that she knows of third graders using it in their classrooms. [10] Scientists can and have used CRISPR to modify genes in many different cell types from many different species, including non-viable human embryos, human cell lines, monkeys, dogs, pigs, mice, yeast, fruit flies, worms, fish, plants, fungi and microorganisms. [4, 10, 11] As noted above, using CRISPR for human germline editing raises a number of ethical issues and has created considerable controversy [1, 5], but ethicists are right to point out that the use of CRISPR to edit the genomes of non-human species should also be considered carefully if there is potential or intent for the altered organisms to be released into the wild. [9, 12, 13]

Bioethicists often turn to traditional principles of beneficence/non-maleficence, autonomy, and justice to evaluate bioethical questions [14, 15], and principlism will be fruitfully employed here to examine ethical issues relating to the use of CRISPR. The ability to edit genomes may also give rise to questions about the proper role of humans, a theme that has previously been explored vis-à-vis genetic human enhancement, perhaps most notably by Michael Sandel. [16] Environmental stewardship, defined by the U.S. Environmental Protection Agency as "the responsibility for environmental quality shared by all those whose actions affect the environment"[17], is also relevant in evaluating uses of CRISPR. For example, many people believe that present-day societies should leave the Earth in a condition such that future generations of humans will be able to enjoy and prosper from our natural world.

Beneficence/ Non-maleficence

Evaluating CRISPR on basic principles of beneficence (do good) and non-maleficence (do no harm) may actually be quite difficult given the uncertainties involved. [1] Many agree that under the right circumstances, using CRISPR to modify defective genes in somatic cells of individuals with genetic disorders, in the aims of curing the disease, is worth pursuing. [18] These genetic changes would not be heritable. Experimentation in animal models will be necessary to ensure that the risks of trying it in humans are justified by potential benefits, but if benefits are deemed greater than risks by both review boards and individual research subjects, this type of gene editing seems ethically sound.

Making heritable changes to the germline, such as removing the predisposition for a genetic disease from an embryo, raises more complex ethical questions. [19] As Baltimore *et al.* write, "Even this seemingly straightforward scenario raises serious concerns, including the potential for unintended consequences of heritable germline modifications, because there are limits to our knowledge of human genetics, gene-environment interactions, and the pathways of disease."[1] Evaluation of benefits and risk must take into account the availability of alternative approaches to reach the same goal. Preimplantation diagnosis (PGD) can often be used to select embryos that do not harbor a disease-causing genetic variant carried by one or both of the parents, but there are scenarios in which two partners who desire to have a biological child may not be able to use PGD to remove an undesirable gene from fertilized embryos. [5, 20] For example, they may both have mutations in both copies of the same autosomal recessive gene. For some, this scenario may justify the use of gene editing a human embryo if certain safety criteria are met. [6] Others may think that the benefits do not exceed the risks, because the couple could become parents of a healthy child through adoption or using a donor egg or sperm. Some people may hold firm to a belief that genetic manipulation of human embryos is never justified because it violates the sanctity of human life. Even those who support human germline editing may have divergent views about exactly which genes are fair game: some may say therapeutic uses of CRISPR editing would be ethical, but enhancement would not be. [e.g.,16] However, blurred lines between therapy and enhancement will further complicate matters.

There is also much discussion in the literature about combining the power of CRISPR gene editing with genetically engineered 'gene drives.' [2, 3, 10, 13, 21] Gene drives, which can add genetic material to an organism or be designed to inactivate certain genes, are inherited in a dominant, non-Mendelian fashion such that the genetic change is passed down to most progeny. [10] One might think of gene drives as a "mutagenic chain reaction."[3, 10] If the genetic change affects the ability of an organism to survive, an entire species could theoretically be extinguished. [9, 21] Scientists believe that gene drive technology has the potential to rid environments of mosquitos that harbor disease or halt the damaging effects of invasive plant species. [21] Gene drives might also be used to reverse pest or weed resistance to pesticides or herbicides, respectively. [21] While the intent of these interventions may be good, introducing organisms with gene drives into the wild may have unintended consequences—on the altered species itself, its ecosystem, even the surrounding environment. The reintroduction of wolves in Yellowstone had profound impacts on the ecosystem, and even changed the geography of the river basin. [22] This example demonstrates that changing the numbers of one species can have unforeseen downstream effects (pun intended). Oye *et al.* have cautioned that gene drives intended to target one species may also affect other species if the guide RNA mutates over time, or if species intermate. [13] This issue challenges both the principles of beneficence and non-maleficence, and also relates to questions about the proper role of humans and environmental stewardship, which are discussed further below.

In general, people will want to use CRISPR to "do good" or to prevent harm, when benefits are perceived to outweigh risks. But some people may want to leverage CRISPR technology to intentionally cause harm. [9] CRISPR could be used to manipulate pathogens, such as smallpox or avian H5N1 virus.[9] Although many countries have agreed not to create or store biological weapons as signatories to the Biological and Toxin Weapons Convention, not all countries—or political groups—are party to the agreement. [9] "Moreover, as the tools needed to design and manipulate pathogenic organisms and the exact genetic sequences and instructions to do so become more readily available," Caplan *et al.* write, "the effectiveness of the BWC to prevent the misuse of biological tools and knowledge is increasingly limited."[9] Ill-intentioned use of gene drives to harm agricultural production is also theoretically possible. [13]

Jennifer Doudna, one of the discoverers of the CRISPR-Cas 9 system, first started to worry about the safety of CRISPR when she saw a postdoctoral fellow present work at a conference in 2014. [2] CRISPR had been used to modify an adenovirus to effect genetic changes in the lung tissue of mice. [2, 23] "Doudna got a chill; a minor mistake in the design of the guide RNA could result in a CRISPR that worked in human lungs as well," Ledford writes in a *Nature* news story. [2] Given that CRISPR is known to have issues of specificity (off-target effects), one has to wonder whether it is possible that insertion in human cells might be possible even without a matching guide RNA sequence. This type of risk must also be taken into account when evaluating the beneficence/non-maleficence of different uses of CRISPR.

Autonomy

Questions of autonomy have also been raised about CRISPR, particularly for human germline editing. People born with genetic modifications engineered at an embryonic stage, if there ever are any, would not have the opportunity to consent to the modification. [24] They could withdraw from observation, of course, but the genetic edit itself could not be reversed. [24] In an NIH statement explaining its position not to fund human germline editing, Francis Collins points to "ethical issues presented by altering the germline in a way that affects the next generation without their consent." [25] In an *AJOB* comment, Joanna Smolenski states, "It is not clear at present how research on germline modification in humans could be pursued in light of the substantial difficulties in ensuring adequate consent not only on the part of the experimental subject, but also on the part of the future generations that will be impacted by the intervention." [24]

While it is important to recognize that embryos cannot consent to being modified, completely objecting to modifying embryos on this basis does not seem reasonable. These types of concerns have been overcome in similar, albeit not identical, situations: in the not–so-distant past, IVF and PGD were experimental procedures. While the children born from these procedures are overwhelmingly healthy and the procedures are now widely viewed as safe, they were certainly experimental when first performed. In fact, we are still collecting long-term multi-generational data on children born with assisted reproductive technologies. [26] If anything, the lack of ability for embryos to consent just places more importance on the evaluation of benefits and risks. John Harris has also offered substantive reasons to support his view that "concern about consent is simply irrelevant here." [27]

There is another, more subtle ethical concern relating to autonomy, though, in that the choice of some individuals or societies to use or allow germline gene editing (particularly for enhancement) may not be completely autonomous. In other words, the decision by some to enhance embryos may impinge on others (or at least the environment of others) if the technology confers advantages to those who use it. People can choose to refrain from using the technology themselves, but if others adopt the technology in large numbers, they may feel pressured to use it for their children to keep pace. When interviewed by *Nature*, Annelien Bredenoord offered potential societal risks of CRISPR that included "public pressure to use this technique *(which would reduce rather than enhance autonomy)* [emphasis added]; how to pay for this technology; how the use of the technology for enhancement would affect society."[20] In the future, there may be a genetic modification that enables individuals to have a longer lifespan, for example. If the majority of people choose to edit this change into the genomes of their progeny, those who may not have supported the use of genetic editing for human embryos will face a new ethical quandary: either edit the embryos of their own progeny or be content that their children will have shorter-than-average lifespans.

Justice

Many bioethicists are also concerned that CRISPR technology, if used for therapeutic or enhancement purposes, may not be equitably available for everyone to use. [19, 20] This would further exacerbate the inequalities between haves and have-nots. Chan *et al.* write, "As with most emerging biomedical technologies, human genome editing raises substantial concerns about justice and equity, such as questions about for whom treatments are developed and who will have access."[28] Further, some worry that protections for disabled individuals may weaken if disabilities are viewed as a choice rather than chance. [29] If society became less willing to take care of individuals with disabilities as a result of the availability of gene editing technology, this could also be considered a threat to justice.

Proper Role for Humans

Sandel has famously made the argument that making edits to enhance human genomes would challenge "the proper stance of human beings toward the given world." [16] Sandel presents the dichotomy between human obligations to accept what is given and to work to transform what is given to make it better. [16] He argues that gene editing for enhancement purposes would be misguided because it would push the focus of human intention too far towards transforming rather than accepting our children as they are. [16] Sandel's thesis might also be applied to the use of gene editing to modify the world at large… how much of the environment should we accept as is? How much should we seek to change? Does it matter if we are trying to rid the world of malaria (akin to a therapy) or if we are trying to create more nutritious foods (akin to enhancement)? Perhaps in a similar vein, Charo and Greely caution that humans should not be carefree about making genetic changes to non-human animals: "Even those not reflexively against 'unnatural' changes through biotechnology might find something unsettling about altering the biosphere with uses that are recreational, whimsical, or even Disneyfied."[12]

Environmental Stewardship

In environmental ethics, the concept of stewardship is an important one. Many believe we should leave the Earth in a condition such that future generations will be able to thrive and prosper. There is no doubt that humans can impact the natural environment. [see discussion in 12] Climate change as brought on by the industrial revolution is a ready example of the scope and speed with which human activity can wreak irreversible changes on our biosphere. With CRISPR, humans have an unprecedented ability to direct genetic changes in living organisms, including our own species. As Nicholas Wade wrote in the *New York Times*, if changes to the human genome are "sufficiently extensive" they "might, in principle, alter the nature of the human species." [5] We may have foreknowledge that genetically modifying living creatures will cause changes in our environment, but we must acknowledge our incomplete understanding of the effects our actions may have. As Jackson Allen wrote in the *Harvard Science Review*, genome editing with CRISPR gives "humanity the power to control its own evolution at the genetic level—not to mention the ability to change the genetics of the animals and plants that inhabit our world."[30] Yes, we may have the power to control, but we don't have complete control, and we don't have complete understanding of the world we live in, or even how a particular gene functions.

Concluding Thoughts

The fact that CRISPR gives us the capability to irreversibly alter our own universe without full knowledge of what we are doing should give us pause. We may not foresee all risks, so we must take care when evaluating the beneficence/non-maleficence of our actions. Perhaps Sandel is right when he says humans must strive to strike the right balance between transforming and accepting. [16] This does not necessarily mean that human germline editing should never be performed or that genetically modified organisms should never be released into the wild. But the synthesis of all the ethical concerns highlighted in this essay, including issues relating to beneficence/non-maleficence, autonomy, justice, the proper role for humans, and environmental stewardship, certainly calls for us to proceed cautiously and slowly when we look to transform our world with this powerful technology known as CRISPR-Cas9.

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