Articles

Gene Drives and Genome Modification in Nonhuman Animals: A Concern for Informed Consent?

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Abstract: In recent years, CRISPR-Cas9 has become one of the simplest and most cost-effective genetic engineering techniques among scientists and researchers aiming to alter genes in organisms. As Zika came to the fore as a global health crisis, many suggested the use of CRISPR-Cas9 gene drives in mosquitoes as a possible means to prevent the transmission of the virus without the need to subject humans to risky experimental treatments. This paper suggests that using gene drives or other forms of genome editing in nonhumans (like mosquitos) for the purposes of disease prevention raises important issues about informed consent. Additionally, it examines the consequences this line of inquiry could have for the use of gene drives as a tool in public health and suggests that the guidance offered by informed consent protocols could help the scientific community deploy gene drives in a way that ensures that ongoing research is consistent with our ethical priorities.

Keywords: CRISPR-Cas9; gene editing; gene drives; informed consent; public health; genetic engineering; genome modification; Zika

In recent years, CRISPR-Cas9 has become one of the simplest and most cost-effective genetic engineering techniques among scientists and researchers aiming to alter genes in organisms. This ease of use and relatively low cost has raised concerns that it could be used to edit the human germ line—a move attempted in 2015 by researchers in China that was met with near unanimous disapproval throughout the international scientific community. Elsewhere, I have argued that, in addition to potential harm, one substantive ethical issue raised by germ line editing is its inability to fit in to our established informed consent protocols.[1] This alone gives us prima facie justification to avoid research in this domain, at least until such issues can be adequately addressed.

However, as Zika came to the fore as a global health crisis, many suggested the use of CRISPR-Cas9 gene drives in mosquitoes as a possible means to prevent the transmission of the virus without the need to subject humans to risky experimental treatments. Despite such potential utility, this paper suggests that using gene drives or other forms of genome editing in nonhumans (like mosquitos) for the purposes of disease prevention also raises important issues about informed consent and asks whether extant informed consent protocols can give us any guidance about how to handle such issues. Additionally, it examines the consequences this line of inquiry could have for the use of gene drives as a tool in public health. I propose that concerns similar to those that emerge about informed consent in cases of human germ line modification also arise with respect to the use of gene drives and genome modification in nonhuman animals. First, gene drives alter organisms in ways that could impact the health of human communities. In addition, the benefits are not guaranteed. Lastly, I will argue that the guidance offered by informed consent protocols could help the scientific community deploy gene drives in a way that protects potentially vulnerable groups and helps ensure that ongoing research is consistent with our ethical priorities.

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What Is Genetic Engineering and Why Pursue It?

Genetic engineering refers to "a wide range of techniques by which scientists can add genetically determined characteristics to cells that would not otherwise have possessed them."[2] Although a large number of techniques fall under the umbrella of genetic engineering—including mitochondrial transfer, somatic-cell nuclear transfer (SCNT), zinc-finger nucleases (ZFNs), and transcription activator–like effector nucleases (TALENs)—the discussion here focuses on clustered regularly interspaced short palindromic repeat–associated system, or CRISPR. CRISPR is "a bacteria-derived system that uses RNA molecules that recognize specific human DNA sequences. The RNAs act as guides, matching the nuclease to corresponding locations in the human genome. CRISPR-Cas9 is the simplest genome-editing tool to work with because it relies on RNA-DNA base pairing, rather than the engineering of proteins that bind particular DNA sequences."[3]

CRISPR-Cas9 has been the focus of much discussion in the genetic engineering realm because it is the simplest gene-editing tool currently available. As it does not rely on traditional reproductive methods or mouse models, modifications can be introduced directly into embryos without intermediate steps. This also makes CRISPR simpler to adapt and incorporate into different research contexts because it does not depend on engineered proteins, the development of which is both cumbersome and costly.[4] As a result, CRISPR is also far less expensive than existing alternatives. While ZFNs could cost upwards of $5,000 per use, CRISPR can cost as little as $30 per use.[5] This lower cost leads to more opportunities for experimentation, which in turn results in greater potential for developing therapeutic applications or beneficial gene drives.

Indeed, much of the research in this domain is oriented around disease and public health applications. For example, in April 2017, researchers used CRISPR to develop a platform called SHERLOCK, which was able to detect specific strains of viruses like Zika and dengue, as well as pathogenic bacteria.[6] This incredibly sensitive and rapid diagnostic tool is one million times better at detecting specific genetic material than the currently most common alternative and so makes it "easier to find infections or cancer mutations that less sensitive diagnostics can miss."[7]

In addition to increased diagnostic precision, genetic engineering also aims to treat, eliminate, or prevent disease. The past several years have seen clinical developments using genome editing seeking treatments and cures for diseases like HIV/AIDs, hemophilia, sickle cell anemia, and some cancers.[8] Also, CRISPR-Cas9 gene drives in mosquitoes are seen as a way to potentially prevent the transmission of viruses, including malaria, "by adding, disrupting, or editing genes or . . . propagating traits that reduce reproductive capacity."[9] Such drives aim to render virus-carrying female mosquitoes sterile and thus unable to transmit the virus to future generations, thereby minimizing infection in humans.[10] The hope is that genetic interventions like these will alleviate much of the burden long-term illnesses present for health care systems and patients by producing "one and done . . . genetic fixes [that] would last the lifetimes of the modified cells."[11]

However, genetic engineering can be subdivided into two general categories based on the types of cells that are modified: somatic or germ line. Somatic gene modification "consists of introducing a gene or gene segment into specific tissues or organs (excluding germ line cells or reproductive cells) in a human subject . . . [that] does not alter the genetic makeup of future generations because the altered

gene does not exist in reproductive eggs or sperm."[12] The aim here is to repair or eliminate a mutation that is causing a disease for the lifetime of the individual carrying it. Germ line gene modification, on the other hand, is a more controversial technique because the introduction of a gene into germ line cells will result in heritable changes that affect offspring.[13] The goal of germ line editing is to modify cells at the embryonic level so that the changes will be inherited by future generations and not limited to the particular individual.

Somatic Versus Germ Line Gene Modifications

Genetic modification is still a relatively new field of scientific research whose implications need to be handled carefully. Unfortunately, the ensuing debate about its permissibility has collapsed what are presently taken to be important distinctions. For example, while one of the first comprehensive ethical studies of genetic engineering—President Carter's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1982 report entitled *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings*—focused primarily on somatic gene modification, the anxieties it responded to about "tampering with nature" or "playing God" seem more germane to modifications of the germ line.[14]

Historically, there has existed an ethical boundary between somatic and germ line gene editing, which is supported by near-unanimous international consensus in legislation. With genetic technology still in its early stages, many countries do not have explicit legislation in place permitting or forbidding its use, considering such research experimental and not therapeutic. However, of the 21% of the world's nations with policies in place regarding inheritable genetic modification, it has been "prohibited by law or by measures having the force of law" in every instance. This consensus is most visible in Western Europe, where 68% of its nations prohibit the modification of the germ line.[15]

Whether there is a philosophically-justifiable bright-line between somatic and germ line modification is an open question beyond the scope of this paper. However, as there already exists de facto international consensus that endorses such a distinction, the burden of proof seems to rest with those suggesting that we defy this agreement and move forward with germ line modifications regardless. Consensus in this domain is particularly important, as so-called reproductive travel—wherein people travel beyond their native borders to obtain reproductive services that are illegal or impermissible in their home countries—is already widely practiced among those with the means and a sufficiently strong desire to achieve their reproductive goals. People committed to pursuing all possible technologies to reproduce will not be deterred by legislation forbidding particular procedures in their own jurisdictions. As a result, there is a threat that pursuing germ line modification in defiance of international consensus will have an impact far beyond national borders.

The same is true of the pursuit of germ line modification in nonhuman animals and insects. Gene drive technology will inevitably "affect the global commons," as population-level changes are difficult to restrict to the regions where they have been approved. Continued reproduction among genetically modified organisms can cross international jurisdictions in (possibly) noncontainable ways. As such, policies enacted in one nation can have consequences for trade partners,

bordering states, and other unwilling parties. Also, with gene editing technologies advancing more rapidly than they can be regulated, the resulting scientific marketplace can incentivize risk-taking and boundary pushing. In cases where gene drives are used to inhibit reproduction, as has been imagined with mosquitoes, these reduced populations' sizes could result in a reduction of genetic diversity. Such consequences could be enduring, even if the genome changes were reversible in individual organisms.[16] Those advocating the pursuit of this technology would have to accept the globalized consequences of such a decision and realize that many of the impacted parties will not have consented to its use. This is particularly problematic in light of the acknowledged necessity, in other domains, of acquiring informed consent from those who participate in experimental research.

Germ Line Modification and Informed Consent

Because participation in medical research is supererogatory, it is crucial to ensure that anyone who engages in it has a thorough understanding of the risks and benefits of their participation and provides informed consent. Elsewhere, I have argued for the difficulty in assimilating human germ line modification into our extant informed consent protocols.[17] The focus here, however, is on nonhuman cases, which may seem strange at first. After all, scientists frequently conduct research on nonhuman organisms, and surely no one thinks we need (or could possibly obtain) informed consent from those various animals or insects in order to legitimately undertake those studies. However, many of the applications of nonhuman germ line modification have a similar intended purpose not only to human genetic modification, but also to vaccination. Just as vaccines have been used to eradicate disease (e.g., smallpox) and prevent disease transmission (e.g., influenza), technologies like gene drives have been intended to do the same with respect to diseases like malaria, dengue, and Zika. If informed consent is required for vaccination, it is plausible to suppose it could also be required for nonhuman genetic interventions that serve an analogous function.

Additionally, citizens increasingly want to have a say in their environments, particularly when it is likely to affect their health. We need look no further than the outcry within some groups against genetically modified organisms, or GMOs, to see that many people have a strong resistance to their consumption, largely due to anxiety that GMOs might be more harmful than organic produce. Also, there has been an increase in civilian resistance to polluting industries entering new markets, as when hundreds of protesters gathered outside of a solar panel manufacturing plant in Haining, China that was alleged to have let solid waste contaminate a neighboring river. According to Ma Jun, the director of Beijing's Institute of Public and Environmental Affairs, there was a growing sense that people have rights over what happens in their communities and that environmental pollution is important in individual health outcomes.[18]

These concerns are best exemplified in the case of Key Haven, Florida, which was "the site of a proposed field trial of a mosquito genetically modified in ways that would allow researchers to locally and temporarily suppress the population of a species of mosquito, *Aedes aegypti*, which transmits dengue, Zika, and chikungunya." Only 34.84% of Key Haven residents approved the trial in Key Haven; they ultimately rejected the idea of serving as guinea pigs for the release of the genetically modified mosquitoes. As one petition put it: "We don't consent to be

part of the trial [*sic*]."[19] Not only did the members of this community seek to exercise their right to determine how the environment in which they live could be altered, their protest also suggested a shared concern that this alteration could have an adverse impact on their health, even as it was intended to potentially stymie the spread of viral disease.

Because gene drives alter organisms in ways that could impact the health of human communities, it is important for their constituents to understand the risks and benefits of allowing such technology to be introduced. They should also be apprised of their rights, the motivation behind both the study and its localization in their community, and what exactly undertaking the study entails. Given that all of these are required elements of informed consent protocols, I suggest that applying these standards to such cases can help us make sense of how to pursue nonhuman gene modification in a morally responsible way.

After all, communities can be substantially impacted by the organisms that live in them, sometimes in unforeseeable ways. For example, consider an innovation like antibiotic medicine, which has had a hugely positive impact on human health by preventing bacterial infections. However, over time it has also led to unanticipated antibiotic resistance and more potent strains of bacteria. Given the pressing public health issue that has resulted from such resistance and the likelihood of it getting worse before it gets better, one might wonder whether we would have chosen such widespread dissemination of antibacterial products had we known about the possible consequences in advance.

This counterfactual is of particular concern in the case of CRISPR gene drives. "In late 2015, researchers reported a CRISPR gene drive that caused an infertility mutation in female mosquitoes to be passed on to all their offspring. Lab experiments showed that the mutation increased in frequency as expected over several generations, but resistance to the gene drive also emerged. . . . Just as antibiotics enable the rise of drug-resistant bacteria, population-suppressing gene drives create the ideal conditions for resistant organisms to flourish."[20] In light of the speed with which gene drive resistance emerged in this case, it is reasonable to assume that this could emerge as a substantial problem, were gene drives to be utilized more broadly. Would we want to potentially reproduce the antibacterial resistance problem with respect to malaria, dengue, or Zika?

However, one might object that, unlike in cases of prospective human germ line modification, gene drives can be accompanied by specific reversal drives. These "could overwrite unwanted changes introduced by an initial drive or by conventional genome engineering, even restoring the original sequence." Given the potentially vast impact of nonhuman germ line interventions, "before any primary drive is released . . . the efficacy of specific reversal drives should be evaluated."[21] Nevertheless, we do not know the long-term impact of introducing primary drives and then reversal drives—it is possible that there is a risk associated with this back and forth. Additionally, the engineered genes could reproduce more quickly than we could reverse them. After all, according to the Environmental Protection Agency, the typical life cycle of a mosquito is not longer than two weeks, which would leave very limited time for reversing a primary drive once it has been introduced into an environment.[22]

Also, even if the gene drives themselves were reversed, the "ecological effects would not necessarily be reversed."[23] Engineered organisms could profoundly alter ecosystems by changing the natural balance of their components. For example,

resistant organisms could flourish, which would exacerbate the problems we wished to resolve with the use of the gene drives in the first place. As such, it is presently unclear whether these gene drives would actually confer benefit over harm, and interventions are acceptable primarily in virtue of the benefit they confer. This makes it particularly crucial that those who are impacted by the use of gene drives in their communities be made aware of the likelihood of risk and benefit.

The use of CRISPR to alter germ lines, both human and nonhuman, raises concerns because of the possibility of unknowable, serious, or debilitating health issues continuing or worsening through future generations. While the risks associated with the technology are not an in-principle objection to its use, it is a crucial concern at this juncture, particularly in light of consent considerations. The introduction of genes into the germ line is without precedent, and it is unclear how such interventions could develop in future generations.[24] The difficulty in providing adequate information about risk and benefit to community members who might be impacted by germ drives in light of the uncertainty surrounding their downstream effects gives us reason to avoid research in this domain, at least until such issues can be adequately addressed. It is not clear at present how research on germ line modification in humans could be pursued in light of the substantial difficulties in ensuring the safety not only of the experimental subject, but also of the future generations potentially affected by the intervention. As long as gene modification techniques continue to be developed in the years to come, these ethical concerns will continue to arise.

Notes

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