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Gene Drives

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Executive summary

Gene drive technology offers the possibility of bypassing the laws of mendelian inheritance and nearly ensuring the transmission of specific genetic material from a given organism to its offspring. The technology could help address many intractable problems from species conservation to infectious disease transmission. But while the technology has been demonstrated in multiple laboratories, the precise effects of gene drives within wild ecosystems is as of yet uncertain. Given the immense potential of the technology, further research is warranted. But regulation is a must, and public participation in the development of this technology should be increased.

Recommendation

Gene drive research should continue, but the technology is not yet ready for open release. More ecological assessment should accompany field trials, and development should be done in a highly transparent, highly participatory, and highly regulated way.

*Figure taken from: National Academies of Science, Engineering, and Medicine, "Gene Drives on the Horizon."

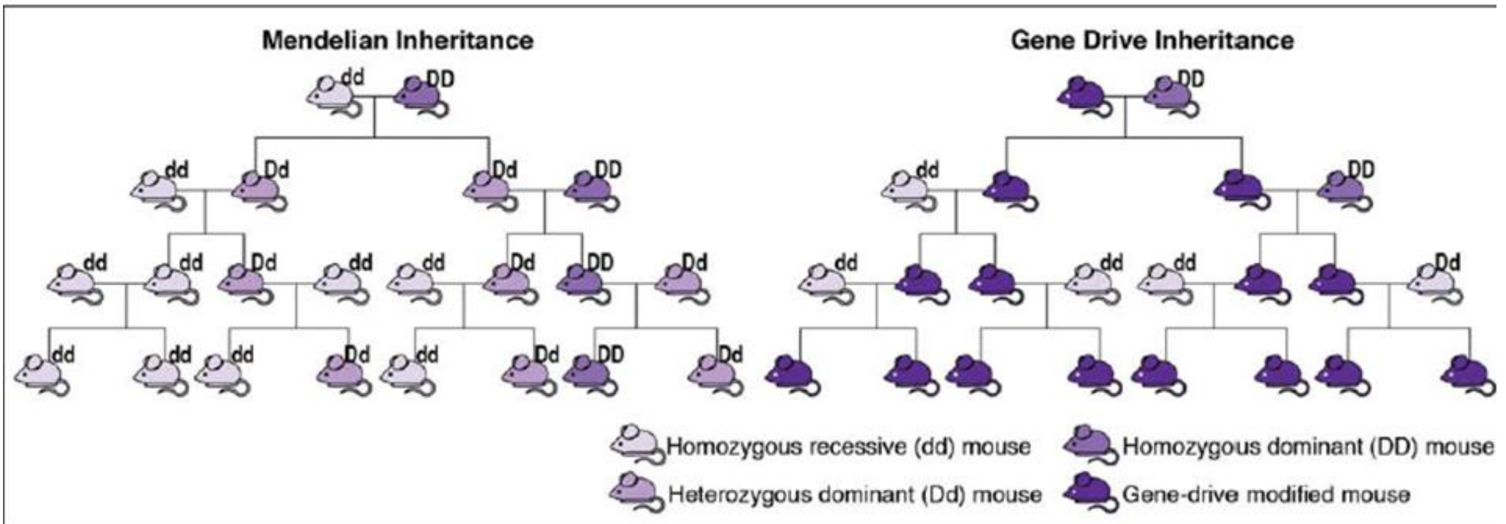

Figure 1. An Idealized Illustration of Mendelian Inheritance versus Gene Drive Inheritance. *Gene drives are often described as an exception to the conventional rules of inheritance first described in 1866 by a monk named Gregor Mendel. Under Mendelian inheritance* (left), *offspring have on average a 50% chance of inheriting a gene (d or D). With a gene drive* (right), *the offspring will almost always receive the targeted genetic element (shown in dark purple), the end result of which is preferential increase of a specific* genotype. *In this idealized illustration, the targeted genetic element is eventually present in 100% of the population, although this may not always occur.*

Introduction

According to the standard laws of Mendelian inheritance, only half of an organism's offspring will inherit any particular gene. This ensures that future generations of a species are similar in composition to previous generations (at least across short time horizons). But capitalizing on the recent discovery of the CRISPR-Cas9 genome editing system, scientists are now able to bypass the laws of Mendelian inheritance and nearly guarantee the transmission of specific genetic material from parent to progeny through the use of *gene drives*. Defined as "systems of biased inheritance that enhance the ability of a genetic element to pass from an organism to its offspring,"[1] gene drives have potentially limitless applications. These applications range from public health interventions, to improved species conservation techniques, to more efficient agricultural practices.[2] But while all gene drives bias inheritance in one way or another, there are significant differences in the drives themselves.

It is useful to group gene drives into one of four different categories that vary along two different dimensions. For instance, gene drives can either be *self-limiting* or *global*, and they can either aim at *suppression* or *replacement* of a given population. Self-limiting gene drives would require continual release of engineered populations in order for the desired trait to spread through and remain in a wild population, whereas global gene drives could, theoretically, push a particular genetic element through a wild population with a single release of an engineered population. And we could select a genetic element that would, for instance, drive sterility through the population, thus leading to population suppression or extinction. Or we could select a desirable genetic element to push through the population that would not lead to suppression, but rather replacement of the wild-type population with the engineered population.

Given the self-limiting / global, replacement / suppression dimensions, the four categories of drives are: (1) global population replacement; (2) self-limiting population replacement; (3) global population suppression; and (4) self-limiting population suppression. Global population replacement would take a desired genetic trait and drive it through the entire population. Self-limiting population replacement would be similar to global population replacement, except there would be a limit to the drive's efficacy. Global population suppression would push a gene through the entire population, a gene that would cause the population to crash. Self-limiting population suppression would have similar effects to global population suppression in the short term, but would be something that we could (again, in theory) limit or control.[3]

Applications

Gene drives have perhaps limitless applications. Below, three potential applications of the technology are briefly highlighted.

Public Health

Many infectious diseases are spread by animal vectors. For instance, malaria, dengue, chikungunya, yellow fever, and zika are all spread by particular species of mosquito. Traditional approaches to controlling such disease vectors have included spraying of insecticides and broad dispersal of insecticide treated nets to protect populations from the infected mosquitoes. While such traditional approaches have saved many lives, progress on eliminating the diseases carried by mosquitoes and other vectors has been declining, in part due to insecticide resistance and in part due to climate change.[4] Gene drives could be used to help control or even eliminate the spread of these mosquito-borne diseases. For example, a replacement drive could be developed with aim of eliminating malaria. A drive for *Anopheles gambiae* mosquitoes could be developed so that the mosquito would be incapable of hosting the parasite. The replacement drive could be pushed through the entire population of *Anopheles gambiae*, thus significantly reducing – and, perhaps, eventually eliminating – the spread of malaria. Similarly, a suppression drive could be aimed at *Aedes aegypti*, the mosquito species primarily responsible for the spread of the zika virus. A sterility gene could be driven through the *Aedes aegypti* population, thus causing a significant or complete population suppression. Without the vector to transmit the disease, zika would likely be eliminated.

Conservation

Gene drives could also be used to further conservation efforts. As in the case of public health, there are myriad ways in which gene drives could serve the cause of conservation. First, gene drives could be used to (1) control organisms that carry diseases that threaten particular species. For example, honeycreepers are birds ingenuous to the Hawaiian Islands. But the honeycreepers are endangered due to avian malaria, which is spread by the *Culex quinquefasciatus* mosquito.[5] As in the case of human malaria, a gene drive could be used to modify the *Culex quinquefasciatus* population so that it is unable to host the parasite, thus saving the indigenous honeycreeper

[1] National Academies of Sciences, Engineering, and Medicine, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values* (Washington, D.C.: National Academies Press, 2016), https://doi.org/10.17226/23405.

[2] For an interesting example of an application, see the section on conservation below.

[3] For more on this typology, see: Daniel Edward Callies, "The Ethical Landscape of Gene Drive Research," *Bioethics*, August 6, 2019, https://doi.org/10.1111/bioe.12640.

[4] World Health Organization, "World Malaria Report 2017" (Geneva: World Health Organization, 2017).

[5] National Academies of Sciences, Engineering, and Medicine, *Gene Drives on the Horizon*.

population. Second, gene drives could be used to eliminate invasive species that threaten biodiversity on islands. For example, the house mouse *Mus musculus* has been introduced to many islands, where it inhibits various native species from reproducing and generally has a negative effect on island ecosystems. The standard procedure for controlling these mouse populations is to widely and repeatedly disperse rodenticides (poisons) that kill the mice. But such dispersal of rodenticides carries its own negative impact on the ecosystem and has many off-target effects. A suppression drive could be used to crash the *Mus musculus* population, in theory preserving island biodiversity without the negative impacts engendered by rodenticides. Finally, gene drives could be used to alter or enhance organisms, making them more resilient to climate change. For example, the American pika is threatened by high summer temperatures – temperatures that are only increasing due to climate change. Luckily, there are small populations of pika living at lower altitudes that have evolved to cope with higher temperatures.[6] A gene drive could be used to pass this genetic element on to all pika populations, allowing them to survive the higher summer temperatures associated with climate change.

Agriculture

Gene drives also have potential application in agriculture. *Amaranthus palmeri*, commonly called pigweed, infests much of the land set aside for agriculture in the Southern United States. Traditionally, *Amaranthus palmeri* has been controlled with the use of herbicides like glyphosate. However, the weed has recently developed resistance to the herbicide, and this resistance is becoming widespread. *Amaranthus palmeri* reproduces sexually, making it a good candidate for a gene drive solution. Either a suppression or a replacement drive could be developed against the weed. A suppression drive could target either the male or female variant of the weed and hinder reproduction. Or a replacement drive could target the weed's resistance to glyphosate, making it susceptible to the traditional herbicide. *Amaranthus palmeri* is only one possible target of a gene drive approach to increase agricultural production. There may be many others as well.

Each of the aforementioned potential applications of gene drive is still only theoretical. There have been significant proofs-of-concept in laboratories, but more research is needed.[7] Still, the potential applications boast such promising social benefits that such research should continue.

Ecological Concerns

The promising potential of gene drives notwithstanding, the technology raises many ecological concerns – two of which are horizontal gene transfer and the potential negative impacts they could have on ecosystems.

Horizontal Gene Transfer

Every gene drive construct would be developed for specific genetic material within a specific species. But there is a worry that the gene drive construct could be transferred horizontally, that is, to a different species – say, humans or an apex predator. Especially given the interest in gene drives that cause sterility or lead to a crash in a population, horizontal gene transfer could have devastatingly negative impacts were it to occur. The possibility for such transfer was studied during the trials of another kind of biocontrol: Wolbachia infection. The studies found no horizontal gene transfer occurred, and that Wolbachia infected mosquitoes were safe to be released.[8] But Wolbachia is significantly different from gene drives, and more studies are needed in order to rule out the possibility of horizontal gene transfer before any gene drive construct is ready for open release.

Ecosystem Implications

The implications that any gene drive modified organism has on the ecosystem of which it is a part will vary. As was highlighted above, some gene drive modified organisms may have a positive impact on the ecosystem to which they are introduced by eliminating or controlling invasive species. But there is also a possibility for such gene drive organisms to have negative impacts on ecosystems. Take a drive aiming to suppress or eliminate a given mosquito population, for example. Apart from procuring blood from other animals (something only egg-laying females do), mosquitoes play a role in their respective ecosystem. Many mosquito species are pollinators, landing on flowers in order to feed. And, of course, the mosquitoes themselves provide food for larger predators within the ecosystem, such as birds, bats, and fish and frogs that eat their larvae. Removing mosquitoes from the ecosystem could have devastating effects on the plants, birds, and fish with which they interact. Though, that may not necessarily be true.[9] Evolutionary biologist Olivia Judson points out that there are more than 3,500 species of

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[6] Clare Palmer, "Saving Species but Losing Wildness: Should We Genetically Adapt Wild Animal Species to Help Them Respond to Climate Change?," *Midwest Studies In Philosophy* 40, no. 1 (September 2016): 234–51, https://doi.org/10.1111/misp.12058.

[7] V. M. Gantz and E. Bier, "The Mutagenic Chain Reaction: A Method for Converting Heterozygous to Homozygous Mutations," *Science* 348, no. 6233 (April 24, 2015): 442–44, https://doi.org/10.1126/science.aaa5945; Valentino M. Gantz and Ethan Bier, "The Dawn of Active Genetics," *BioEssays* 38, no. 1 (January 2016): 50–63, https://doi.org/10.1002/bies.201500102; Andrew Hammond et al., "A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector Anopheles Gambiae," *Nature Biotechnology* 34, no. 1 (January 2016): 78–83, https://doi.org/10.1038/nbt.3439.

[8] Timothy P. Hurst et al., "Impacts of *Wolbachia* Infection on Predator Prey Relationships: Evaluating Survival and Horizontal Transfer Between *w* MelPop Infected *Aedes Aegypti* and Its Predators: Table 1.," *Journal of Medical Entomology* 49, no. 3 (May 1, 2012): 624–30, https://doi.org/10.1603/ME11277.

[9] C. M. Collins et al., "Effects of the Removal or Reduction in Density of the Malaria Mosquito, Anopheles Gambiae, on Interacting Predators and Competitors in Local Ecosystems," *Medical and*

mosquito, and only 1% of those are vectors for harmful viruses like dengue and zika. Judson argues that we could eliminate those disease-carrying species without much negative impact on the environment.[10] Still, thorough research would need to be conducted in each locale to determine the specific impact that a gene drive modified organism would have.

Ethical Concerns

Alongside ecological concerns, gene drive technology is almost certainly to carry with it ethical concerns. Below, two such concerns are briefly outlined.

Hubris

One might worry that attempting to harness the kind of genetic control that gene drives promise is hubristic. Dating back to the times of the Hellenic Greece, hubris describes a dangerous overconfidence in one's abilities. The hubris worry related to gene drives could be directed in one of two directions. One might worry that, in attempting to harness such genetic power, we are sure to bring about severe negative side-effects. And taken to the furthest point possible, this worry might still stand no matter how much research is done and no matter how many safeguards are put in place. This kind of hubris worry may be justified. There will almost always been unforeseen negative side-effects of intervening in natural systems on such a fundamental level.[11] Though, that is not to say that the side-effects will be severe. On the other hand, the hubris worry could be grounded not in the negative side-effects that gene drive technology is supposed to bring about. Rather, one could worry that harnessing such genetic power just isn't something we should be doing, regardless of whether or not we could do so without engendering negative side-effects.[12] Perhaps it's the idea of intentionally eradicating species that might raise intrinsic objections, or perhaps it's the very idea of modifying a genome that has developed across millions of years. Either way, some will almost certainly find the research and development of gene drives objectionable.

Slippery Slope Concerns

Even if one does not find the research of gene drives objectionable in and of itself, there could still be a slippery slope concern. One could worry that research into gene drives will inevitably lead to the deployment or release of gene drive modified organisms. If one is worried that research into, for instance, gene drive modified mosquitoes will lead to their eventual release, the worry is probably well-placed. There are multiple laboratories currently researching gene drive mosquitoes, and it seems likely that they will be field tested and perhaps even cleared for open release at some point in the near future. If, however, the slippery slope concern is that research into gene drive modified mosquitoes will lead to a kind of dystopia in which all genomes, including human genomes, are completely designed in the lab, then the concern is more farfetched.[13] There are various ways to regulate and control the development of gene drives such that the valuable public health, conservation, and agricultural goals can be researched, without such research leading to a completely designed world. In fact, incorporating public values and public say into the research process – something that is addressed below – can go some way towards assuaging slippery slope concerns.

Political Concerns

Alongside ethical concerns about gene drives lie a number of political concerns. Two such concerns are the potential transboundary issues gene drive modified organisms could raise, and, as previously alluded to, how to incorporate the pubic into the research and development of the technology.

Transboundary Issues

Many of the populations of organisms that could be modified with gene drives do not reside exclusively within one political territory or another. Rather, these populations cross political boundaries uncontrollably. This creates a significant political problem when neighboring countries have different policies regarding gene drives.[14] Even if the possibility of a gene drive modified organism crossing political boundaries is faint, it is still a possibility that should be accounted for. Local and national governments where research is being conducted should work with neighboring governments to ensure that containment is a priority and that contingency plans are in place should transboundary issues arise.

Procedural Concerns

Finally, how the substantive decisions regarding gene drives are made is of the utmost importance. Most researchers agree that there is a need for public engagement when it comes to gene drive research and development. But exactly what that engagement should look like gives rise to divergent visions. Often, the public is divided into different categories. There are those immediately affected communities where gene drive modified organisms could be released; there are groups of stakeholders with varying

Veterinary Entomology 33, no. 1 (March 2019): 1–15, https://doi.org/10.1111/mve.12327.

[10] Olivia Judson, "A Bug's Death," *The New York Times*, September 25, 2003, https://www.nytimes.com/2003/09/25/opinion/a-bug-s-death.html.

[11] Holger Hoffmann-Riem and Brian Wynne, "In Risk Assessment, One Has to Admit Ignorance," *Nature* 416, no. 6877 (2002): 123.

[12] Michael J. Sandel, *The Case against Perfection: Ethics in the Age of Genetic Engineering* (Cambridge, Mass: Harvard University Press, 2007).

[13] Callies, "The Ethical Landscape of Gene Drive Research."

[14] For more on transboundary issues as they relate to genetically modified mosquitoes, see: World Health Organization, "Guidance Framework for Testing of Genetically Modified Mosquitoes" (Geneva, Switzerland, 2014).

interests related to gene drive research and development; and then there is the broader public who may not be directly affected, but nonetheless has in interest in gene drive technology.[15] What counts as appropriate public engagement will depend upon the public under consideration and the particular research that is being conducted. For instance, some kind of community consent might be required before field testing in a given area can be conducted.[16] But consent of the broader public may not be obligatory for responsible research to go forward. While the precise form and manner of public engagement may be tough to identify in the abstract, it is undoubtedly an essential component of responsible research.

Conclusion

Gene drive technology has immense potential. The technology could help address many intractable problems from species conservation to infectious disease transmission. But while the technology has been demonstrated in multiple laboratories, the precise effects of gene drives within wild ecosystems is as of yet uncertain. Given the immense potential of the technology, further research is warranted. But that research should be conducted with the relevant ecological, ethical, and political concerns in mind. Regulation is a must, and public participation in the development of this technology should be increased.

[15] National Academies of Sciences, Engineering, and Medicine, *Gene Drives on the Horizon*.

[16] Pamela A. Kolopack and James V. Lavery, "Informed Consent in Field Trials of Gene-Drive Mosquitoes," *Gates Open Research* 1 (December 11, 2017): 14, https://doi.org/10.12688/gatesopenres.12771.1.