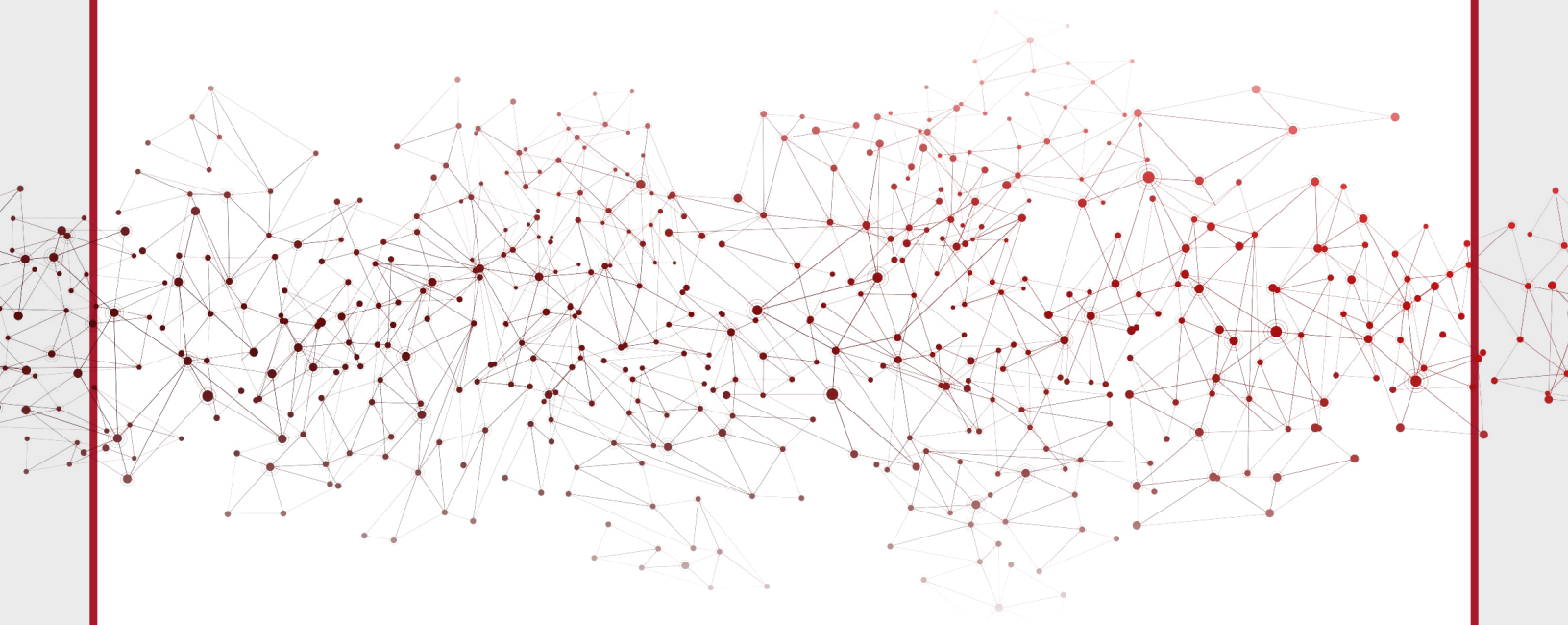
TECHNOLOGY FACTSHEET SERIES

Gene Drives



CONTRIBUTORS:

Jeantine Lunshof, Harvard

Carmel Shachar, Harvard

Rey Edison, MIT

EDITOR:

Amritha Jayanti

HARVARD Kennedy School

BELFER CENTER

for Science and International Affairs

Technology & Public Purpose Project

The Technology Factsheet Series was designed to provide a brief overview of each technology and related policy considerations. These papers are not meant to be exhaustive.

Technology and Public Purpose Project

Belfer Center for Science and International Affairs
Harvard Kennedy School
79 John F. Kennedy Street, Cambridge, MA 02138

www.belfercenter.org/TAPP

Design and layout by Andrew Facini

Executive Summary

Gene drives can be defined as genetic elements that pass from parents to unusually high numbers of their offspring due to biased inheritance (sometimes referred to as the possession of "selfish" genetic elements).[1,2] There are different ways of achieving this biased inheritance needed for a drive, but the shared outcome is one where the offspring of a parent carrying a certain genetic variant has over a 50% likelihood of inheriting it. With regular inheritance, in the absence of a gene drive, each of the two alleles carried by a parent are equally likely to be inherited by offspring.

By implementing modern gene editing technology, such as CRISPR, gene drives can be manufactured by humans to intentionally suppress a target population or spread a trait through a population. For example, gene drives could be used to target weeds, spreading a trait that would reverse their evolved resistance to non-toxic herbicides. Gene drives could also be used for human health purposes, in particular for the control of vector-borne diseases, such as malaria through populations of mosquitos.

There are many outstanding governance questions with regards to the specific research, development, testing, and deployment of gene drives—including who should be taking ownership of drafting regulations and policy. At this stage, few countries currently have regulations that are defined specifically for gene drive, and in most countries the closest relevant regulations are those written for a broader swath of gene editing technologies. As there becomes more momentum around the potentially unique opportunities of gene drives though, it is important for U.S. legislators and policymakers to remain engaged in the technology's technical, ethical, and practical progress and consider technology-specific governance.

What is a Gene Drive?

A gene drive does not, by definition, need to involve genetic engineering. There are many natural examples of gene drives, and scientists have considered applications of these naturally occurring drive systems as early as the 1940s.[3] However, gene editing technology, such as CRISPR-Cas9—a technological advancement in gene editing that provides a molecular tool for altering regions of DNA[4]—can be used to build

1 Collins, Cynthia H. "Gene Drive." Scientific American. Scientific American, September 14, 2018. https://www.scientificamerican.com/article/gene-drive1/.

2 "Gene Drives on the Horizon." The National Academies of Sciences, Engineering, Medicine, 2016. https://research.ncsu.edu/ges/files/2017/11/jri-si-nas-gene-drives-horizon-full-2016.pdf.

3 J. Min, A. L. Smidler, D. Najjar, and K. M. Esvelt, "Harnessing gene drive," Journal of Responsible Innovation, vol. 5, no. sup1, pp. S40–S65, Jan. 2018.

4 Collins, James P. "Gene Drives in Our Future: Challenges of and Opportunities for Using a Self-Sustaining Technology in Pest and Vector Management." BMC Proceedings 12, no. S8 (July 19, 2018). https://doi.org/10.1186/s12919-018-0110-4.

self-propagating gene drives that would allow humans to intentionally and precisely alter or suppress various species.[5] Recent experiments demonstrate that a CRISPR-based gene drive can spread a targeted gene throughout almost all laboratory populations of yeast, fruit flies, and mosquitos. Engineered gene drives can be used (1) to **alter** populations or (2) to **suppress** populations, depending on the use case.

Because a gene drive is designed to spread, a major concern is that using a gene drive outside of the laboratory—or even within the laboratory—without adequate biosafety measures may cause the gene drive to spread to organisms outside the target population. For this reason, there is increased interest in designing and using gene drives that are intentionally designed to limit their activity over time, such as the so-called *daisy drives*,[6,7] or over space, such as so-called *threshold-dependent gene drives*[8,9], in contrast to gene drives that are indefinitely self-propagating. Many self-limiting gene drives have been modeled, but the extent to which such designs effectively limit themselves in laboratory or field populations is still largely undetermined.

Key Benefits and Applications of Gene Drive

There are many ways to utilize the ability of gene drives to suppress or spread a trait through a population. Gene drives could be used to target weeds, spreading a trait that would reverse their evolved resistance to non-toxic herbicides. This could reduce the need to use newer and more toxic herbicides, which could have both cost-saving and environmental benefits. Another approach could be to suppress populations of species, plant or animal, that cause agricultural damage, reducing the need to use pesticides or herbicides. Similarly, gene drives could be used to remove populations of invasive species that cause damage to ecosystems or economies.

Gene drives can also be used for human health purposes, in particular for the control of vector-borne diseases. A population of a species that carries or transmits disease could be targeted with gene drives for suppression, so that the population is no longer large enough to effectively spread disease. Alternatively, for some species there may be a way to use gene drive to spread a specific (engineered) trait throughout the population so that the trait prevents organisms in the population from being disease vectors.[10,11]

---

5 Ibid.

6 C. Noble et al., "Daisy-chain gene drives for the alteration of local populations," Proc. Natl. Acad. Sci. U. S. A., vol. 116, no. 17, pp. 8275–8282, Apr. 2019.

7 S. Dhole, M. R. Vella, A. L. Lloyd, and F. Gould, "Invasion and migration of spatially self-limiting gene drives: A comparative analysis," Evolutionary Applications, vol. 11, no. 5. pp. 794–808, 2018.

8 J. M. Marshall and B. A. Hay, "Confinement of gene drive systems to local populations: a comparative analysis," J. Theor. Biol.

9 O. S. Akbari, K. D. Matzen, J. M. Marshall, H. Huang, C. M. Ward, and B. A. Hay, "A synthetic gene drive system for local, reversible modification and suppression of insect populations," Curr. Biol., vol. 23, no. 8, pp. 671–677, Apr. 2013.

10 J. Champer, A. Buchman, and O. S. Akbari, "Cheating evolution: engineering gene drives to manipulate the fate of wild populations," Nat. Rev. Genet., vol. 17, no. 3, pp. 146–159, Mar. 2016.

11 K. M. Esvelt, A. L. Smidler, F. Catteruccia, and G. M. Church, "Emerging technology: concerning RNA-guided gene drives for the alteration of wild populations," Elife, vol. 3, p. e03401, 2014.

Agricultural	Environmental	Human Health
• Target weeds to reverse evolved resistance to non-toxic herbicides • Suppress pests for sustainable and humane pest management	• Removing invasive species that cause economic or ecological damage • Conservation of threatened or endangered species	• Reduction or elimination of insect or rodent-borne disease by targeting primary vector

Technological Capabilities and Limitations

Recently, a method for creating gene drive in mammals, mice in this case, was demonstrated in the laboratory.[12,13] However, most existing methods for generating gene drives were developed and tested in laboratory or caged populations of insects such as fruit flies (*Drosophila*) and species of the malaria vector mosquito, *Anopheles stephensi* and *Anopheles gambiae*.[14] Additional methods for creating drive have also been proposed but not yet demonstrated in the lab.[15,16,17]

Gene drive can only be used in species that reproduce sexually, and are best-suited to species that reach sexual maturity rapidly and thus have a short generation time. This is because gene drives act when organisms reproduce, so gene drives spread slowly in long-lived organisms, and spread rapidly only in short-lived species. In general, preliminary estimates suggest gene drives will generally take several dozen generations to spread to all organisms of a given species in the targeted region.

Predicting efficacy depends on assessing a gene drive's evolutionary stability, which describes the extent to which the gene drive's functioning may be impaired by evolutionary processes in the population in the specific environment being targeted.[18] For instance, the effects of the gene drive may include a fitness cost to the organism, and more fit alleles may outcompete the gene drive, despite its enhanced rate of inheritance. That is, even if the gene drive allele is more likely to be inherited, organisms with another allele may be

12 H. A. Grunwald, V. M. Gantz, G. Poplawski, X.-R. S. Xu, E. Bier, and K. L. Cooper, "Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germline," Nature, vol. 566, no. 7742, pp. 105–109, Feb. 2019.

13 Y. Yan and G. C. Finnigan, "Development of a multi-locus CRISPR gene drive system in budding yeast," Sci. Rep., vol. 8, no. 1, p. 17277, Nov. 2018.

14 V. M. Gantz et al., "Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi," Proc. Natl. Acad. Sci. U. S. A., vol. 112, no. 49, pp. E6736–43, Dec. 2015.

15 "Daisy-chain gene drives for the alteration of local populations."

16 T. A. Prowse, F. Adikusuma, P. Cassey, P. Thomas, and J. V. Ross, "A Y-chromosome shredding gene drive for controlling pest vertebrate populations," Elife, vol. 8, Feb. 2019.

17 A. Burt and A. Deredec, "Self-limiting population genetic control with sex-linked genome editors," Proceedings of the Royal Society B: Biological Sciences, vol. 285, no. 1883. p. 20180776, 2018.

18 F. Gould, "Broadening the application of evolutionarily based genetic pest management," Evolution, 2008.

more likely to survive and create more offspring. Another possibility is that an allele may evolve and become immune to the effects of the gene drive, taking away the gene drive's enhanced rate of inheritance.[19,20,21]

One measure of a gene drive's efficacy is its threshold, which is defined as the number of organisms, often written as a percentage of the target population size, that would need to be released into the target population for the drive to spread as intended.[22] The threshold may be affected by fitness costs to an organism carrying the alleles being spread, and such fitness costs do not necessarily show up in laboratory environments, where the organism's needs are provided by researchers. Another factor affecting the threshold of a drive may be the pattern of gene flow within or between populations, which may cause certain drive designs to spread at rates not predicted by idealized models. Threshold does not only affect a drive's efficacy—it also determines how easily the gene drive may spread outside of its target population. A high threshold drive will not easily invade another population unless a correspondingly large number of organisms migrate. As such, risk management strategies need to incorporate research into how a specific population functions in its actual ecosystem in order to assess the likelihood of unintended ecological consequences resulting from the spread of the gene drive.

Current State of Governance and Regulation

The United Nations Convention on Biological Diversity (CBD) has considered a moratorium on gene drive research several times. This happened most recently in November 2018, but the CBD only went so far as to urge caution in field testing.[23] Signatories to the CBD are required to "establish or maintain means to regulate, manage, or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health." Therefore, the CBD pushes its signatories to regulate technologies such as gene drives by considering both environmental and health concerns.

As of May 2019, few countries currently have regulations that are defined specifically for gene drive, and in most countries the closest relevant regulations are those written for a broader swath of gene editing technologies, of which gene drives are only a part. This is also true on the international scale. The *Cartagena*

19 "Harnessing gene drive"

20 "Emerging technology: concerning RNA-guided gene drives for the alteration of wild populations"

21 "Broadening the application of evolutionarily based genetic pest management"

22 "Invasion and migration of spatially self-limiting gene drives: A comparative analysis"

23 Callaway, Ewen. "UN Treaty Agrees to Limit Gene Drives but Rejects a Moratorium." Nature, November 29, 2018. https://doi.org/10.1038/d41586-018-07600-w.

Protocol on Biosafety to the Convention on Biological Diversity[24] is an international treaty among 171 parties. It covers procedures for moving living organisms produced by gene editing from one country to another. The *Nagoya Protocol* is a supplement to the treaty that addresses access to genetic resources and the sharing of benefits when genetic resources are moved from one country to another. Both the *Cartagena Protocol* and the *Nagoya Protocol* are therefore relevant to gene drives by ultimately setting regulations around the flow and transfers of gene drive technology within host species, even though neither is specifically about gene drive. The United States did not sign on to either the *Cartagena Protocol* or the *Nagoya Protocol*. Additionally, there is also some guidance from other international entities, such as the World Health Organization's *Framework for Testing Genetically Modified Mosquitos*.

Additionally, the technology's ranging use cases—whether that be crop yield, health benefits, or species control—have made it difficult for various nation states to know how to categorize gene drives for the purpose of regulation. Often, national governments run into the issue of whether to categorize gene drives as livestock, pest control, or drugs. This has resulted in confusion around regulation leadership and ownership, and what domestic regulations actually apply to the technology.[25]

Public Purpose Considerations

Currently, a small number of organisms with a gene drive exists in laboratories. Much research still needs to be done on their efficacy, safety, and impacts before testing and ultimately using them outside the lab. Whether and how gene drives will be used outside of laboratories depends on the outcomes of tests under conditions of containment, and on how developments proceed in a number of areas, including science, policy, commerce, and public opinion. These areas include, but are not limited to:

- *Technical efficacy* – Understanding robustly whether gene drives spread through naturally occurring or agricultural populations in a way that is similar to how they spread in laboratory trials.

- *Containment* – Understanding whether gene drives can be implemented such that they do not invade or impact non-target populations, and, if so, how this can be achieved.

24 Biosafety Unit. "About the Protocol." The Biosafety Clearing-House (BCH). Secretariat of the Convention on Biological Diversity, May 29, 2012. https://bch.cbd.int/protocol/background/.

25 Oye, K. A., K. Esvelt, E. Appleton, F. Catteruccia, G. Church, T. Kuiken, S. B.-Y. Lightfoot, J. Mcnamara, A. Smidler, and J. P. Collins. "Regulating Gene Drives." Science 345, no. 6197 (2014): 626–28. https://doi.org/10.1126/science.1254287.

- *Ownership* – Deciding whether gene drives and the technologies they depend on are set up to be broadly available and used by many innovators, or whether the technology will be accessible only a select few chosen by patent holders or qualified personnel.

- *Control* – Considering what licensing is required to develop or use the technologies, and if licenses can be obtained for commercial use.

- *Assessment and authorization of trials* – Deciding who determines when any test outside of laboratory confinement can be initiated, and under what criteria and assessment standards.

- *Decision-making* – Taking into account the potential long term and widespread impacts, and who can and/or should have a voice in deciding on the trial and use of these technologies e.g. local community members, government actors, NGOs, etc.[26]

- *Access, rights, and cost* – Considering which communities are given access first access to public health interventions involving gene drive, who has the right to potential health benefits, and who holds the financial burden.

- *Biosecurity* – Acknowledging the biosecurity risks e.g. that gene drives may spread unintentionally across international borders, and releasing a self-spreading technology into another country may be perceived as an act of biowarfare.

- *Biodiversity* – Weighing the biodiversity risks e.g. using gene drives to remove a population or even a species of organisms is itself an ecological consequence, and may have other effects on the biodiversity of the area. It is important to consider who and what determines which invasive species should be removed and over what geographical area.

26 T. O. Harvey-Samuel, K. J. Campbell, M. Edgington, and L. Alphey, "Trialling gene drives to control invasive species: what, where and how?," Island invasives: scaling up to meet the challenge, no. 62, p. 618, 2019.

APPENDIX A:

Key Questions for the Legislation and Regulation of Gene Drive

Many gene drives will likely involve gene editing in their initial creation or in their intended function, and will be covered by existing regulations for gene editing in the United States, though additional regulations may be considered to cover drives produced without gene editing as a separate category. Some of these regulations require containment, but may not be sufficient to regulate a technology that is by nature designed to spread. Regulators and legislators may need to consider questions more specific to gene drives:

1. Scientific and Technical Effectiveness and Safety

Effectiveness

- Has the type of drive being proposed demonstrated to be effective in the laboratory setting?

Laboratory safety

- Should there be a pre-registration process for research projects involving gene drive?
- Are additional biosafety standards needed for research projects involving gene drives?

Biosecurity

- Should regulations address the possibility of dual use e.g. the malicious use of gene drives?

2. Legal and Regulatory Oversight and Control

Patents and Ownership

- What technologies can be patented?
- What applications can be patented?
- What will be done to protect against monopolistic control of gene drive technology?
- What public policy considerations should patent owners be required to take into consideration when implementing these technologies?

3. Licensing and Controls

- Will commercial sale of organisms containing gene drives for consumer or commercial release be permitted?
- Will commercial sale of services involving the release of organisms containing gene drives be permitted?
- What will be the penalty for unauthorized gene drive research or use?
- Considering that it is difficult to reverse the impact of released organisms containing gene drives, should there be heightened controls or penalties?

4. Product Liability and Damages

- What is the liability and punitive damages for accidental release of a gene drive?
- Will liability include long-term ecological damages, and how will these be assessed?
- Will liability include the cost of reversing or counteracting the gene drive (if possible), and what is the management mechanism for implementing such strategies?
- If damage to an ecosystem crosses international borders, how will liability and punitive damages be handled?

5. Acceptable Use

Applications

- When will gene drives be permissible for 1) reducing incidence of disease, 2) species conservation, 3) reducing costs of production, 4) making production more environmentally sustainable or human, 5) delivering new and improved products to consumers? And by whom?
- How will acceptable use be decided? By owners of the technology, regulators, experts, impacted communities, or the public?

Consideration of Alternatives

- Will there be a requirement for considering alternatives to gene drive and comparing the risks and benefits of each?

6. Monitoring and Data

Monitoring Requirements

- Should there be any requirements for ecological or genetic monitoring before, during, and after gene drive release?

- Who is responsible for paying for monitoring? Who does the monitoring?

- What data is collected during monitoring? Genomes of individual organisms? Whether tested organisms contain the gene drive? General information about the population (size, distribution, etc.)?

Data accessibility

- If data is collected during monitoring, who gets access and how frequently must data be made available?

- Do local communities or publics have a right to data or analyses describing local ecosystems? Which data or analyses and how will it be made accessible?

APPENDIX B:

Due Diligence Questions for Investors in Companies

1. Technical Standards

- Is the gene drive targeting gene(s) that are species-specific? Is the target population nearby other populations of the same species?
- What type of gene drive is being proposed?
- Is the gene drive designed to be self-limiting or self-propagating? At what threshold does the gene drive need to be released for it to spread throughout the population?
- Are there proposed methods to counteract evolved resistance to the gene drive?
- Are there proposed strategies for reversing or counteracting the gene drive in case of unintentional release or spread?
- How well is the ecology of the target region understood?
- Are laboratories in compliance with biohazard, biosecurity, and other protocols? Have all staff received appropriate training and certification for their specific duties?

2. Markets

- Who are the intended beneficiaries of the gene drive's effects?
- How large is the overall potential market for the proposed type of gene drive?
- How much does each implementation of the gene drive cost?
- What is the relevant cost-benefit of using a gene drive compared to alternative interventions?
- Who are the competitors providing alternative interventions? What are their interests and current activities?

3. Regulatory Environments

- Where will in-lab research be conducted? Where will outside-of-lab trials be conducted?

- With respect to gene drive, what current permissions and prohibitions exist in the country where research or trials will be conducted?

- In this country, what is the risk the current political or regulatory environment will change before or during laboratory research or trials?

4. Stakeholder Consideration

- What is the public opinion on gene editing and ecological interventions in the regions where the proposed trials will occur? What particular questions or concerns are being discussed in the public discourse?

- What are the opinions of major stakeholder groups (biologists, ecologists, public health experts, environmental advocacy organizations) on this application of gene drive?

- What actions are being taken to make special considerations for effects on vulnerable populations?

HARVARD Kennedy School

BELFER CENTER

for Science and International Affairs

Technology & Public Purpose Project