REPORT IN BRIEF

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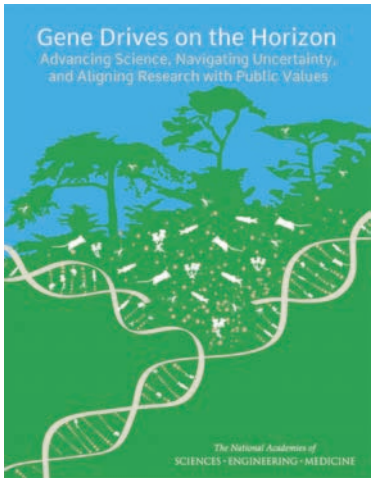
DIVISION ON EARTH AND LIFE STUDIES

Gene Drives on the Horizon

Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values



Gene-drive modified organisms hold promise for addressing difficult-to-solve challenges, such as the eradication of insect-borne infectious diseases and the conservation of threatened and endangered species. However, proof-of-concept in a few laboratory studies to date is not sufficient to support a decision to release gene-drive modified organisms into the environment. The potential for gene drives to cause irreversible effects on organisms and ecosystems calls for a robust method to assess risks. A phased approach to testing, engagement of stakeholders and publics, and clarified regulatory oversight can facilitate a precautionary, step-by-step approach to research on gene drives without hindering the development of new knowledge.

Gene drives are systems of biased inheritance that enhance the ability of a genetic element to pass from an organism to its offspring through sexual reproduction (see Figure 1, p. 2). A wide variety of gene drives occur in nature. Researchers have been studying these natural mechanisms throughout the 20th century but, until the advent of CRISPR/Cas[1] for gene editing, have not been able to develop a gene drive.

Since early 2015, laboratory scientists have published four proofs-of-concept showing that a CRISPR/Cas9-based gene drive could spread a targeted gene through nearly 100% of a population of yeast, fruit flies, or mosquitoes. Biologists have proposed using gene drives to address various public health, agricultural, conservation, and other problems where solutions are limited or entirely lacking (see Box 1). Most research to date is focused on controlling or altering organisms such as mosquitoes that transmit infectious diseases to humans.

The fast-moving nature of the field is both encouraging and concerning. Thus, the National Institutes of Health (NIH) and the Foundation for the National Institutes of Health (FNIH)[2] asked the National Academies of Sciences, Engineering, and Medicine to convene a committee with a broad range of expertise to investigate the state of knowledge regarding gene drives and considerations for their responsible use.

CHARTING HUMAN VALUES

A range of questions about responsible science—from whether, why, and how research should be conducted to whether, when, and where a gene-drive modified organism should be released into the environment—rest on human values at every step.

Perspectives on the place of human beings in ecosystems and their larger relationship to nature have an important role in emerging debates about gene drives. Even

1 CRISPR (**C**lustered **r**egularly-**i**nterspaced **s**hort **p**alindromic **r**epeats) are segments of bacterial DNA that, when paired with a specific guide protein, such as Cas9 (**C**RISPR-associated protein 9), can be used to make targeted cuts in an organism's genome.

2 The Defense Advanced Research Projects Agency and the Bill and Melinda Gates Foundation provided funding to NIH and FNIH, respectively, in support of this study. The study received additional support from the National Academy of Sciences Biology Fund.

as researchers endeavor to reduce the transmission of infectious disease through gene drives, the ability to alter and perhaps to eliminate wild species will be intrinsically objectionable to some people. Proposals to use gene drives in ways that might lead to the extinction of species will require especially careful review.

Widely-shared commitments to protecting human welfare and the environment call for public policy guidelines that may constrain research on gene drives or the release of gene-drive modified organisms. Integrating precautionary measures into the research process can help to balance potentially conflicting commitments.

ECOLOGICAL AND ENVIRONMENTAL CONSIDERATIONS

Research on the molecular biology of gene drives has outpaced research on population genetics and ecosystem dynamics, two fields essential for assessing the efficacy of gene drives and their biological and ecological outcomes. There are considerable gaps in knowledge in regard to ecological and evolutionary considerations for the organism and its ecosystem, including the potential off-target (within the organism) and non-target (in other species or the environment) effects of gene drives.

Generally speaking, a gene drive would likely pose the greatest threat to an ecosystem if it caused inadvertent harm to a native keystone species[3], but the potential effects on the ecosystem might be judged beneficial if a gene drive-modified organism is used to control an invasive species. Unintended consequences should be considered, especially in regard to the risk of transfer to non-target species. In order to address gaps in knowledge, gene drive research will require collaboration of life and social scientists in multiple fields of study.

PHASED TESTING AND SCIENTIFIC APPROACHES TO REDUCING POTENTIAL HARMS

Before field testing or environmental release of gene-drive modified organisms, it is crucial to establish a detailed understanding of the target organism, its relationship with its environment, and potential unintended consequences. It is also essential to consider confinement and containment strategies to reduce the potential for unintended releases.

A phased testing pathway, such as the one outlined by the World Health Organization (WHO) for testing genetically modified mosquitoes, can facilitate a step-by-step approach to research on gene drives.[4] Each step in such a pathway promotes careful study and evaluation, includes checkpoints to determine whether and when research should move to the next phase, and provides vital data to inform and enhance the effectiveness of other potential phases.

THE NEED FOR ECOLOGICAL RISK ASSESSMENTS

Ecological risk assessment is needed in the context of gene drive research. Ecological risk assessment allows comparisons among alternative tactics, incorporates the concerns of relevant publics, and can be used to identify sources of uncertainty, making it well suited to inform research directions and support public policy decisions about emerging gene-drive technologies. Two key features of ecological risk assessments are: (1) the ability to trace cause-and-effect pathways and (2) the ability to quantify the probability of specific outcomes. Environmental assessments and environmental impact statements required by the National

3 Any species whose effect on its ecosystem is disproportionate to its relative abundance.

4 WHO (World Health Organization). 2014. The Guidance Framework for Testing Genetically Modified Mosquitoes. World Health Organization, Programme for Research and Training in Tropical Diseases [online].

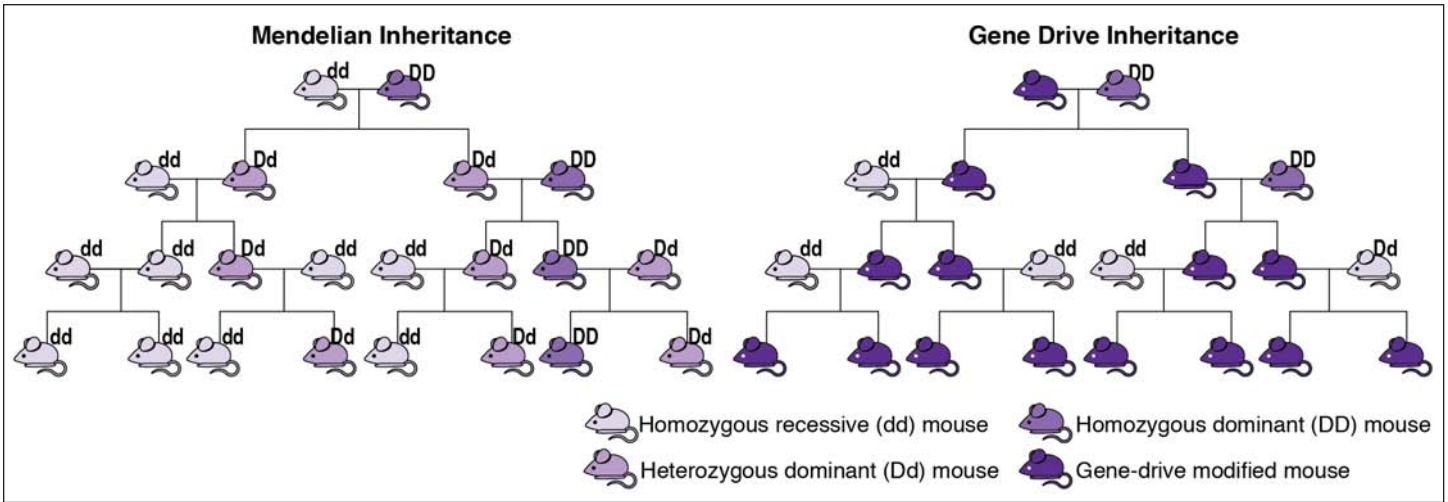


Figure 1. An Idealized Illustration of Mendelian Inheritance versus Gene Drive Inheritance. *Gene drives are often described as an exception to the conventional rules of inheritance first described in 1866 by a monk named Gregor Mendel. Under Mendelian inheritance (*left*), offspring have on average 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.*

Table 1 Potential Applications for Gene Drive Research

Public Health 	• Control or alter organisms that carry infectious diseases that affect humans, such as dengue, malaria, Chagas, and Lyme disease • Control or alter organisms that directly cause infection or disease, such as Schistosomiasis • Control or alter organisms that serve as reservoirs of disease, such as bats and rodents
Ecosystem Conservation 	• Control or alter organisms that carry infectious diseases that threaten the survival of other species • Eliminate invasive species that threaten native ecosystems and biodiversity • Alter organisms that are threatened or endangered.
Agriculture  Fruit damage from spotted wing drosophila infestation	• Control or alter organisms that damage or carry crop diseases • Eliminate weedy plants that compete with cultivated agriculture
Basic Research  DNA Double Helix	• Alter model organisms as part of research on gene-drive function and effects, species biology, and mechanisms of disease

Image sources (top to bottom): US Centers for Disease Control and Prevention, US Fish and Wildlife Service, US Department of Agriculture, National Institutes of Health

Environmental Protection Act, although widely acknowledged as valuable in other contexts, are insufficient tools to characterize the risks of gene-drive modified organisms.

Relevant U.S. guidelines and technical documents are not yet sufficient on their own to guide ecological risk assessment of gene drive technology, because they focus predominantly on evaluating the risks to populations or ecosystems posed by toxic chemicals, and do not yet adequately address assessment of multiple stressors and endpoints or cumulative risk.

ENGAGING COMMUNITIES, STAKEHOLDERS, AND PUBLICS

There is broad agreement on the importance of engaging affected communities and broader publics in decision making about activities involving gene drives. The outcomes of engagement may be as crucial as the scientific outcomes to decisions about whether to release a gene-drive modified organism into the environment. Thus, engagement cannot be an afterthought; it requires effort, attention, resources, and advanced planning.

Mechanisms for public engagement and deliberation already exist within some authorized U.S. agencies that oversee biotechnology, but there is generally little clarity on how public engagement should feed into research and governance and a lack of consensus about best practices in this regard. Governing authorities, including research institutions, funders, and regulators, will need to develop and maintain clear policies and mechanisms for how public engagement will factor into research, ecological risk assessments, and public policy decisions about gene drives

GOVERNANCE OF GENE DRIVES

The governance of research begins with the personal responsibility of the investigator, is formalized in professional guidelines, and often extends to legally binding policies and enforceable regulations. However, some of these mechanisms may be inadequate for identifying potential immediate and long-term environmental and public health implications because they lack clarity in their jurisdiction, are challenged by the distinguishing characteristics of gene drives, or provide insufficient structures for public engagement.

- ***Investigator responsibility and professional guidelines.*** Currently, institutions, funders, and professional societies work in concert to encourage professional best practices in research. Researchers, institutions, and professional societies have the responsibility to maintain and provide education and training in responsible science for gene drive research.
- **Federal Guidelines.** Laboratory-based research funded by the National Institutes of Health (NIH) is subject to NIH's guidelines on biosafety and oversight by Institutional Biosafety Committees (IBCs). Despite decades of providing a robust system of health and environmental protection for laboratory research, IBCs may not yet have the expertise or resources to evaluate the biosafety of gene drives effectively.
- **Federal Regulations.** In the United States, regulation of gene-drive modified organisms will most likely fall under the Coordinated Framework for the Regulation of Biotechnology, which includes the U.S. Food and Drug Administration, the U.S. Department of Agriculture, and the U.S. Environmental Protection Agency. However, the diversity of potential gene-drive modified organisms and contexts in which they might be used reveals a number of regulatory overlaps and gaps. The U.S. government will need to clarify the assignment of regulatory responsibilities for field releases of gene-drive modified organisms, including the roles of relevant agencies

that are not currently included in the Coordinated Framework for the Regulation of Biotechnology.

It is important to note that a one-size-fits-all approach to governance is not likely to be appropriate. Each phase of research activity—from developing a research plan to post-release surveillance—raises different levels of concern depending on the organism being modified and the type of gene drive being developed. Governance and regulation of gene drive research will need to be proportionate to the hazards posed by the specific activity, and evaluated on a case-by-case basis. Because of the existing uncertainties associated with gene drives, regulation will be needed that facilitates fundamental, applied, and translational research so that the potential harms and benefits of gene drives can be explored responsibly in laboratory and field studies.

Potential dual use issues

Gene drive research also raises concerns about biosafety, biosecurity, and potential *dual use* (e.g.,misuse) of the technology. The scientific community has an obligation to work with policy makers to identify and promote best practices to safeguard against unintentional or intentional misuse of gene-drive modified organisms.

Need for international coordination

Responsible governance will need to be international and inclusive, with clearly-defined global regulatory frameworks, policies, and best practice standards for implementation. Low- and middle-income countries where gene-drive modified organisms may be released will need to be involved in governance. In current practice, a significant amount of field research on genetically-modified mosquitoes is conducted under guidelines established by international organizations, such as the WHO, and by the research community itself. These standards should provide a useful foundation for the establishment of guidelines for gene-drive modified organisms.

FUTURE COORDINATION AND COLLABORATION

Although there is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment, the likely benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials.

The report recommends that funders of gene drive research coordinate, and if feasible collaborate, to reduce gaps in knowledge not only about the molecular biology of gene drives, but also in other areas of fundamental and applied research that will be crucial to the responsible development and application of gene drive technology, including population genetics, evolutionary biology, ecosystem dynamics, modeling, ecological risk assessment, and public engagement. The report also recommends that funders of gene drive research establish open-access, online repositories of data on gene drives as well as standard operating procedures for gene drive research.

Considerations for selecting sites for field testing include scientific and technical elements; values of the relevant publics that may be affected; capabilities of local, regional, and national governance bodies; and the ability of researchers to engage with local communities. In site selection, preference should be given to locations in countries with the existing scientific capacity and governance frameworks to conduct and oversee the safe investigation of gene drives and development of gene-drive modified organisms.

Locate information on related reports at http://dels.nas.edu/bls
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The National Academies of Sciences, Engineering, and Medicine appointed the above committee of experts to address the specific task requested by the U.S. Department of Health and Human Services/NIH. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the Academies. This report brief was prepared by the Academies based on the committee's report.

For more information, contact the Board on Life Sciences at 202-334-2187 or visit at **http://dels.nas.edu/bls**. Copies of *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values* are available from the National Academies Press, 500 Fifth Street, NW, Washington, DC 20001; (800) 624-6242; or as free PDFs at **www.nap.edu**.