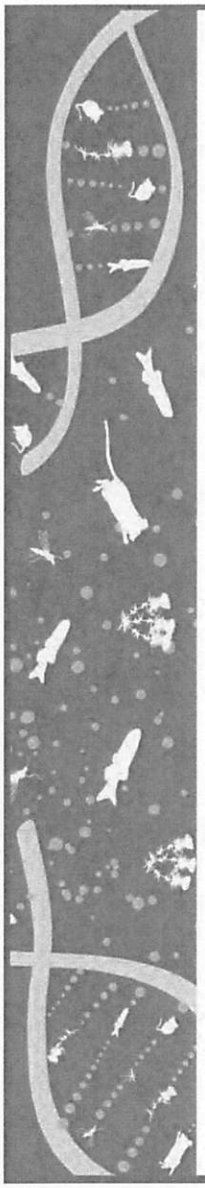

UT Southwestern Medical Center
Ethics Grand Rounds
December 12, 2017

Gene Drives on the Horizon:
Challenges in Science, Ethics, and Governance

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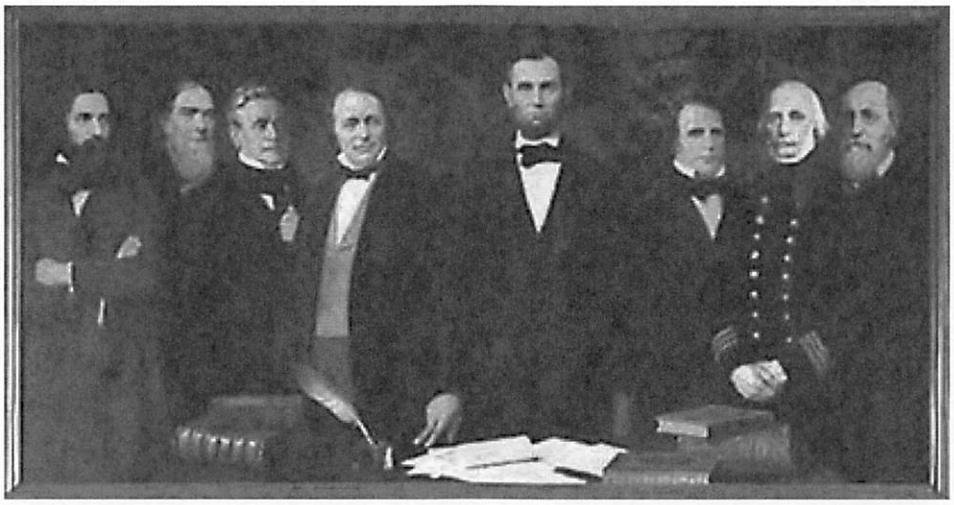
Acknowledgements and Disclosures

- Portions of this presentation were originally prepared for public briefings on the National Academy of Sciences' report *Gene Drives on the Horizon* by Committee members and staff.
- I receive no funding for my work on gene drives. My primary work in research ethics education is funded by the NIH Fogarty International Center and the National Heart, Lung, and Blood Institute.
- I am the Chair of the all-volunteer External Ethics Advisory Committee for the international research project Genetic Biocontrol of Invasive Rodents (GBIRd), funded by DARPA's Safe Genes program.
- [redacted] is the president and majority owner of the privately held company Anesthetic Gas Reclamation, Inc, which has no relation to my work or the current presentation.
- I will NOT discuss any investigational or off-label use of any product.

Objectives

- Introduce National Academy of Sciences' study process and its 2016 consensus report *Gene Drives on the Horizon*
- Outline the science of gene drive research and its challenges for public health, assessment of benefit and harm, and governance;
- Explore ethical values and commitments to protecting human welfare and the environment that may encourage or constrain research on gene drives
- Outline how phased testing and public engagement are essential components of responsible science in gene drive research;
- Recount important events in the field since the release of the NAS report and how they may affect future work in the area.

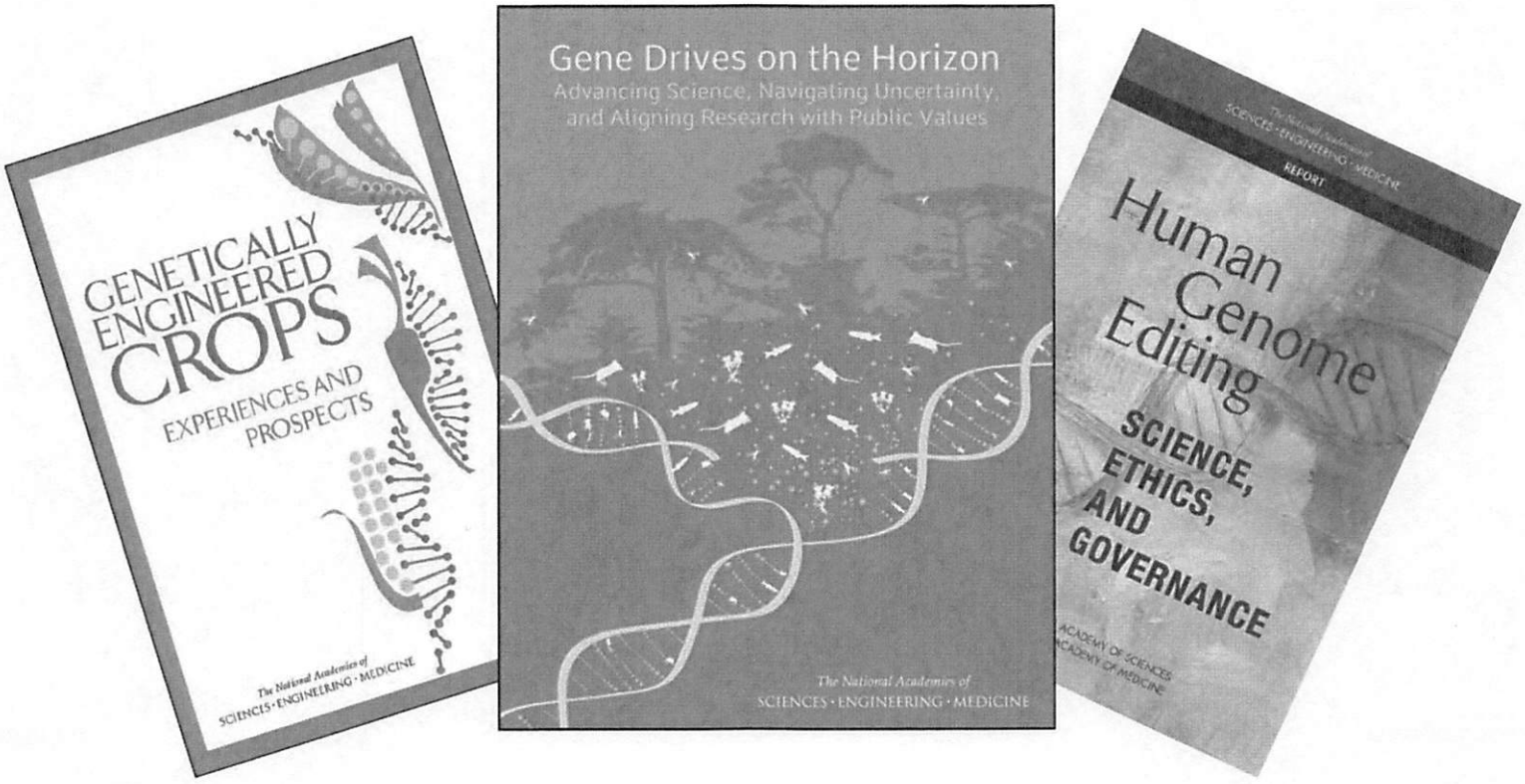
History and Mission of the National Academy of Sciences



Left to Right: Benjamin Pierce; Alexander Bache; Joseph Henry; Henry Wilson; Abraham Lincoln; Louis Agassiz; Charles Henry Davis; Benjamin Gould

"…the Academy shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science or art…"

New techniques in genome editing prompted three related studies in 2015-2016.



Sponsors of the Study on Responsible Conduct of Gene Drive Research in Non-Human Organisms

- The U.S. National Institutes of Health
  - Defense Advanced Research Projects Agency (DARPA)
- The Foundation for the National Institutes of Health
  - The Bill and Melinda Gates Foundation
- The National Academy of Sciences' Biology and Biotechnology Fund

Motivations for the Study

Marked increase in the pace of development and publication of gene drive research after the introduction of CRISPR/Cas9

Speculation about potential uses of future gene drive technology to eliminate pests to human and animal health, agriculture, and specific ecosystems raised questions about ethics and governance

- Could gene drives have unintended consequences for public health and the environment, and if so, what might they be?
- Do we know enough to consider releasing gene-drive modified organisms into the environment? How will we know when we know enough?
- *Should* a gene drive be used to change, suppress or eliminate a pest species?
- How do we decide where gene-drive modified organisms could be released? What should be governments' role in such decisions?

Statement of Task for the Committee on Gene Drives

- Review the **state of the science** of gene drive research, identifying the key scientific techniques for **reducing ecological and other risks,** and characterize and assess environmental and other hazards to target and non-target organisms.
- Examine the **oversight mechanisms** for organisms containing gene drives in the **laboratory**, for use in **field releases within the US and in LMIC**.
- Determine the **adequacy** of the existing **oversight** mechanisms and **risk assessment guidance.**
- Discuss relevant **legal, social or ethical considerations** in selecting sites for field releases and engaging those living in or near potential release sites.
- Provide general principles to guide **responsible practices** in gene drive research.

The report was limited to these questions.

Committee on Gene Drive Research (by expertise)

Biosafety and Biosecurity
Stephen Higgs, Kansas State University

Developmental Biology
Lisa A. Taneyhill, University of Maryland

Ecological Risk Assessment
Wayne Landis, Western Washington University

Entomology and Vector-Borne Diseases
Nicole L. Achee, University of Notre Dame
Lynn Riddiford, Howard Hughes Medical Institute

Ethics and Scientific Integrity in Research
Elizabeth Heitman, *Co-Chair,* Vanderbilt University Medical Center
Gregory E. Kaebnick, The Hastings Center

Plant Biology and Ecology
Vicki Chandler, Minerva Schools at Keck Graduate Institute
Brandon S. Gaut, University of California, Irvine

Population Ecology
James P. Collins, *Co-Chair,* Arizona State University
Joseph Travis, Florida State University
Paul E. Turner, Yale University

Public Interfaces with Controversial Science
Jason A. Delborne, North Carolina State University

Science and Technology Policy and Law
Ann Kingiri, African Centre for Technology Studies
Joyce Tait, University of Edinburgh
David E. Winickoff, University of California, Berkeley

Review Process

Biosafety and Biosecurity
Stephen S. Morse, Columbia University

Molecular Biology
Roger D. Cone, Vanderbilt University

Ecological Risk Assessment
Rebecca A. Efroymson, Oak Ridge National Laboratory

Infectious Disease and Vector Control
Anthony A. James, University of California, Irvine
Robert D. Newman, U.S. Centers for Disease Control and Prevention , Cambodia

Evolutionary Genetics
Austin Burt, Imperial College

Ethics and Responsible Conduct of Science
R. Alta Charo, University of Wisconsin-Madison
Ronald Sandler, Northwestern University

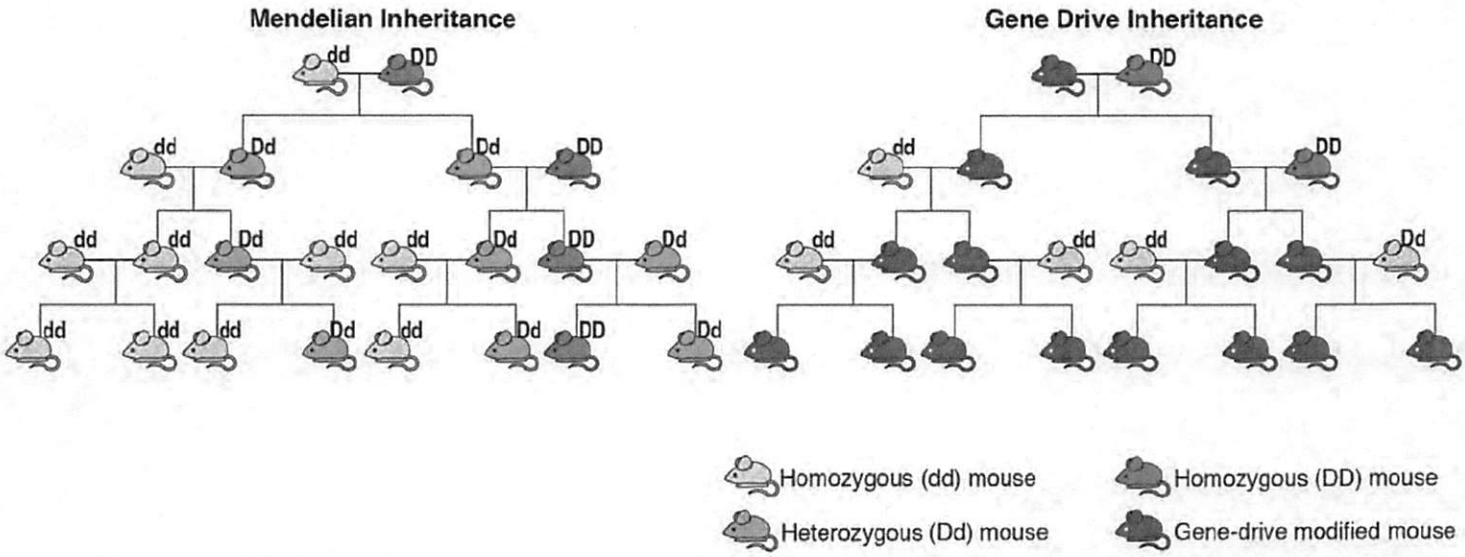
Population and Evolution Ecology
Fred Gould, North Carolina State University
Sarah P. Otto, University of British Columbia

Public and Community Engagement
James Lavery, St. Michael's Hospital & University of Toronto

Science and Technology Policy and Regulation
Calestous Juma, Harvard University
Morven A. McLean, International Life Sciences Institute Research Foundation
Kenneth Oye, Massachusetts Institute of Technology

What Are Gene Drives?

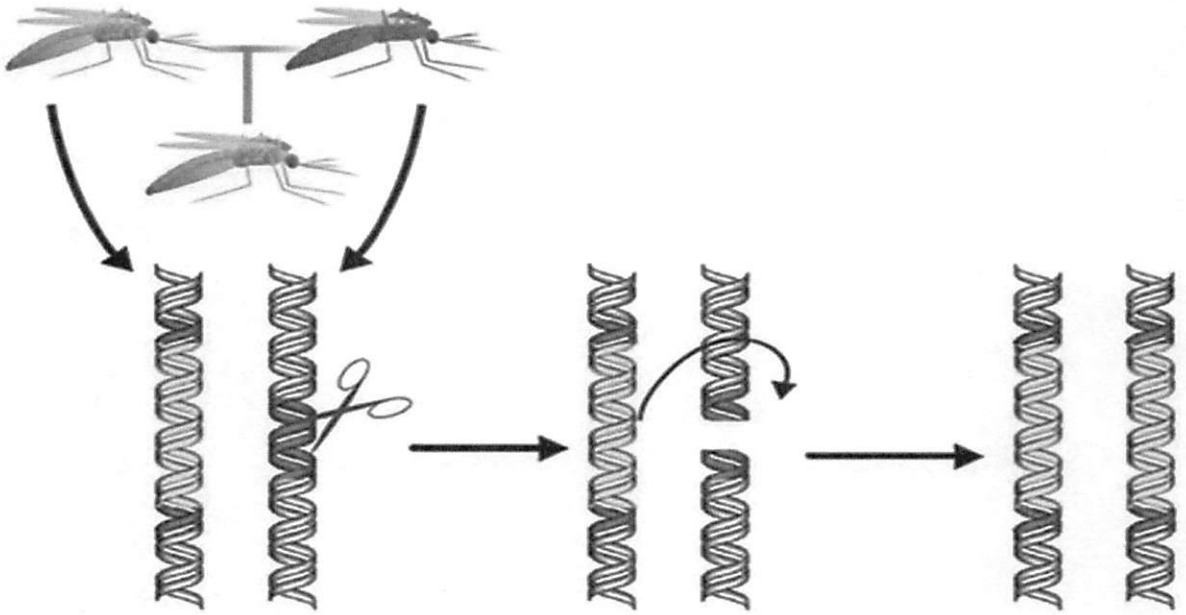
Gene drives are systems of biased inheritance ("selfish genes") that enhance the ability of a genetic trait to pass from a parent organism to its offspring through sexual reproduction.



Basic Facts About Gene Drives

- Gene drives occur in nature in many species
- The "drive" works through various mechanisms
- The phenomenon was first identified in the late 1800s
- Earliest proposals to develop and harness gene drives came in the mid-20th century
- Term "gene drive" first appeared in 1990s
- Technology not available to develop an intentional gene drive until advent of CRISPR/Cas9

CRISPR/Cas9 as a Means to Create a Gene Drive



From Esvelt et al, 2014 https://elife-publishing-cdn.s3.amazonaws.com/03401/elife-03401-v3.pdf

Proof-of-concept studies suggest that gene drives developed with CRISPR/Cas9 could spread a targeted gene through nearly 100% of a lab population of:

- *Saccharomyces cerevisiae* yeast (DiCarlo et al. 2015)
- *Drosophila melanogaster* fruit flies (Gantz and Bier 2015)
- *Anopheles stephensi* mosquitoes (Ganz et al. 2015)
- *Anophenles gambiae* mosquitoes (Hammond et al. 2016)

Early proof-of-concept research is underway to develop an intentional gene drive in *Mus musculus*, the house mouse

Key Features and Potential Uses of Gene Drives

Two key defining features:

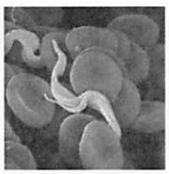
- Spread and persistence in a population
- Potential to cause irreversible ecological change

Two potential uses:

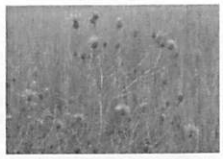
- Population replacement: Change genetic trait(s)
- Population suppression: Decrease numbers, including to possible extinction

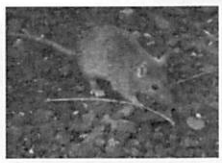
Gene drives have been proposed for various uses

Public Health



Conservation





Agriculture

Basic Research

Criteria for Choosing a Species in Which to Develop a Gene Drive

- Sexual reproduction (get genetic material from 2 parents)
- Short generation time
- Stability of the driving genetic elements and traits
- Population structure and geographic features that facilitate the spread of the gene drive

These features *limit* the applicability of gene drives

Seven Case Studies on Using a Gene Drive:

- Manage dengue transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes
- Combat malaria transmitted by *Anopheles gambiae* mosquitoes
- Combat avian malaria transmitted by *Culex quinquefasciatus* mosquitoes to protect endangered bird species
- Control non-indigenous *Mus musculus* house mice to protect native biodiversity on islands
- Control non-indigenous *Centaurea maculosa* (knapweed) to protect native biodiversity in rangelands and forests
- Increase agricultural production by controlling *Ameranthus palmeri* (pigweed) in fields
- Develop vertebrate models (e.g., *Danio rerio* zebrafish) for basic gene drive research

Conclusions: The State of the Science (Part 1)

There is **insufficient evidence** available at this time to support the release of gene-drive modified organisms into the environment.

However, the **potential benefits** of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials.

There are considerable gaps in knowledge, particularly in regard to ecological and evolutionary considerations for the organism and its ecosystem that in turn affect risk assessments, public engagement, and governance.

Conclusions: The State of the Science (Part 1)

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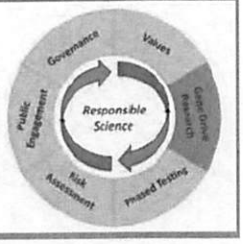
There are considerable gaps in knowledge, particularly in regard to ecological and evolutionary considerations for the organism and its ecosystem that in turn affect risk assessments, public engagement, and governance.

Recommendation 9-1: Funders of gene drive research should coordinate, and if feasible collaborate, to reduce the gaps in knowledge, not only about the molecular biology of gene drives but also in other areas...

The State of the Science (Part 2)



There are considerable gaps in knowledge, particularly in regard to ecological and evolutionary considerations for the organism and its ecosystem that in turn affect risk assessments, public engagement, and governance.

Recommendation 9-2: Funders of gene drive research should establish open access online repositories of data on gene drives as well as SOPs for gene drive research to share knowledge, improve frameworks for ecological risk assessment, and guide research design and monitoring standards around the world.

Responsible Science to Develop Gene Drive Technologies

A responsible science approach to research and development of new technologies calls not only for best technical practices, but also **evaluation of social, environmental, regulatory, and ethical considerations.**

A responsible science approach to gene drive research calls for such continuous assessment on a **case-by-case** basis and **with the input of the people who would be affected** by a release.

Responsible Science Reflects Values at Every Step

Responsible science generally, and responsible conduct of gene drive research specifically, **reflects a complex array of values**, from general questions of why and how gene drive research should be conducted to the specifics of whether, when, and where a gene-drive modified organism could be developed in a lab or released into the environment.

The Committee explored these concepts using a *sociological* understanding of values as deeply held convictions (from many sources) and sources of meaning and importance in one's life. We recognized that important values can be difficult to articulate and are often in tension with other values.

A Dynamic Values Framework

Because the central values of benefits, harms, and justice may be defined differently by different parties, defining them is likely to be a prominent concern in future consideration of gene drives.

Who decides:

- What is a benefit or harm from gene drive research
- Where, how, and when benefits and harms might be distributed

Justice requires that communities and relevant publics must have a say in decisions affecting their welfare

- The definition and identification of benefits and harms must be open-ended, subject to revision through public engagement.

Diverse and Potentially Competing Values May Affect Scientists' and Others' Responses to Gene Drive Research

- Research is often motivated by widely-shared commitments to protecting and enhancing human welfare and/or the world around us. These values support exploring potential opportunities for new knowledge.
- While many people value knowledge that can be used to improve human welfare, many scientists find intrinsic value in the acquisition of new knowledge.
- Still others find intrinsic value in nature and the environment, apart from the benefits or harms that nature may confer to humans or other species.

Gene Drives and Conservation

Proposed uses of gene drives to control invasive species highlight a tension within the conservationist goal of **finding a balance** between **altering nature** to accommodate human demands and **adjusting human demands** to accommodate nature:

- Some regard gene drives as unacceptable alterations to nature
- Others see gene drives as tools that could restore nature, reversing prior changes imposed by humans
- All express Proposals to use gene drives in ways that might lead to the extinction of species will require especially careful review

Reframing Precaution as an Approach to Evidence-Based Decision Making

The Committee addressed the need to weigh the potential benefits, harms, and other values related to gene drive research by recommending a *reframed* precautionary approach to gene drive research.

- NOT the usual view in which the *principle* precaution leads to prevention or prohibition in the event of uncertainty,
- But rather precaution as a **practical element** of responsible science, in which relevant scientific evidence is examined together with stakeholders' values and regulatory precedent to close the gaps of uncertainty.

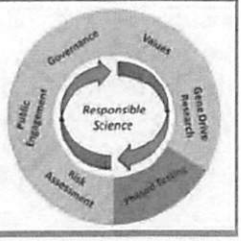
Reframing Precaution in Responsible Science

As the Committee reframed precaution as a **critical attitude to** seeking and generating the kinds of **evidence** that will close the gaps of uncertainty and permit a "go" or "no go" decision on any action.

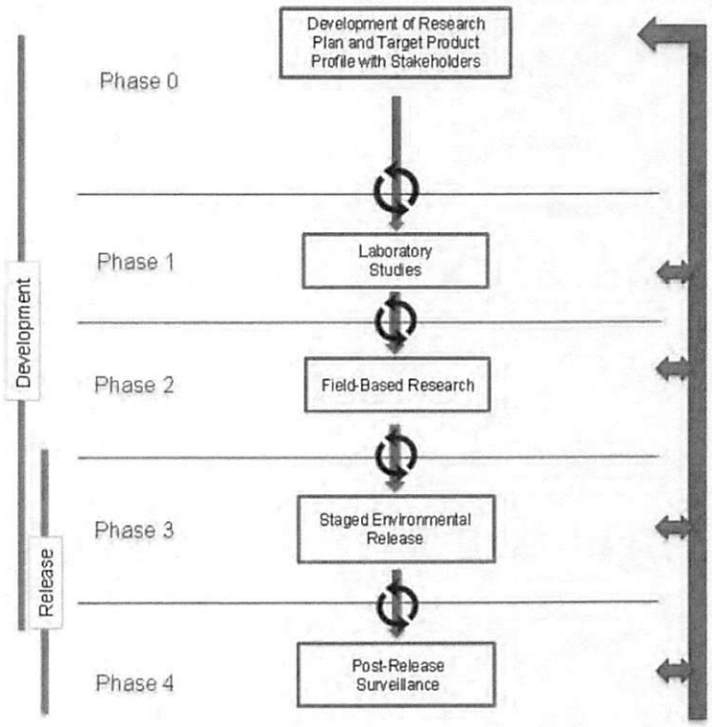
It is not is not an all-encompassing principle for or against action, but a capacity for and commitment to robust assessment that must developed in context.

The Committee concluded that funders and others promote education in the critical assessment required for responsible science, particularly in areas of the world where field research on gene-drive modified organisms is likely to occur.

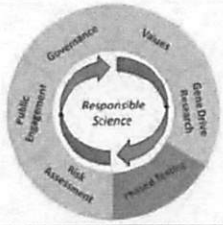
Phased Testing: An Approach to Responsible Science in Practice



Recommendation: Scientists conducting research on gene drives should follow a phased testing pathway, a step-by-step framework that begins with developing a research plan and continues through, if applicable, monitoring gene-drive modified organisms in the environment.

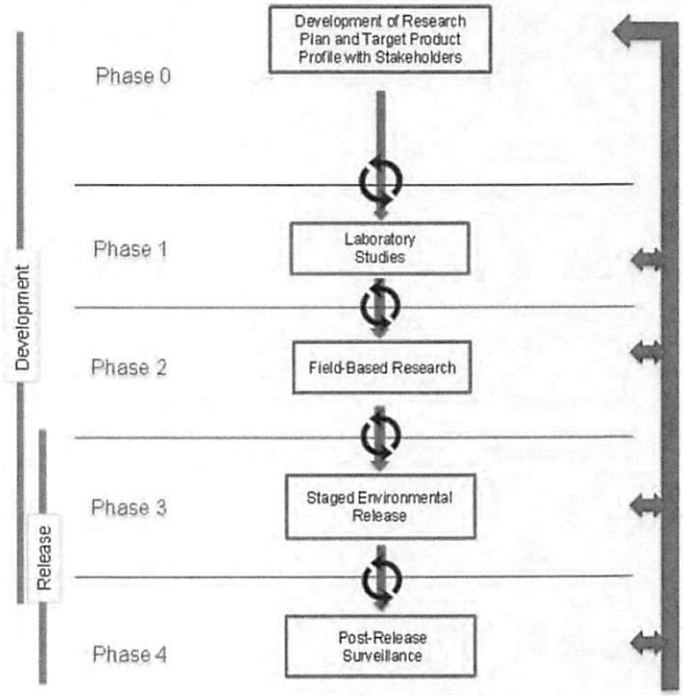


Phased Testing: A Precautionary Approach



Because gene drives are intended to spread and persist in the environment, it is crucial to:

- Understand the target organism, its role in the environment, and potential for unintended consequences such as off and non-target effects
- Develop confinement and containment strategies to minimize unintended persistence or release
- Develop mechanisms to detect and monitor gene-drive modified organisms



Phased Testing: Fundamental safety considerations

Containment is the use of human-made or natural physical restrictions to prevent unintended or uncontrolled *release (escape)* of an organism into the environment (large cages, greenhouses, aquaculture pens; geographic isolation).

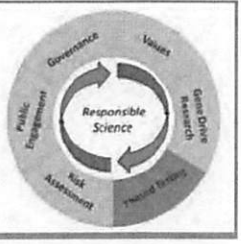
Confinement is the use of ecological conditions or biological methods to prevent unintended or uncontrolled *persistence* of an organism in the environment (e.g., climatic isolation).

Recommendations:

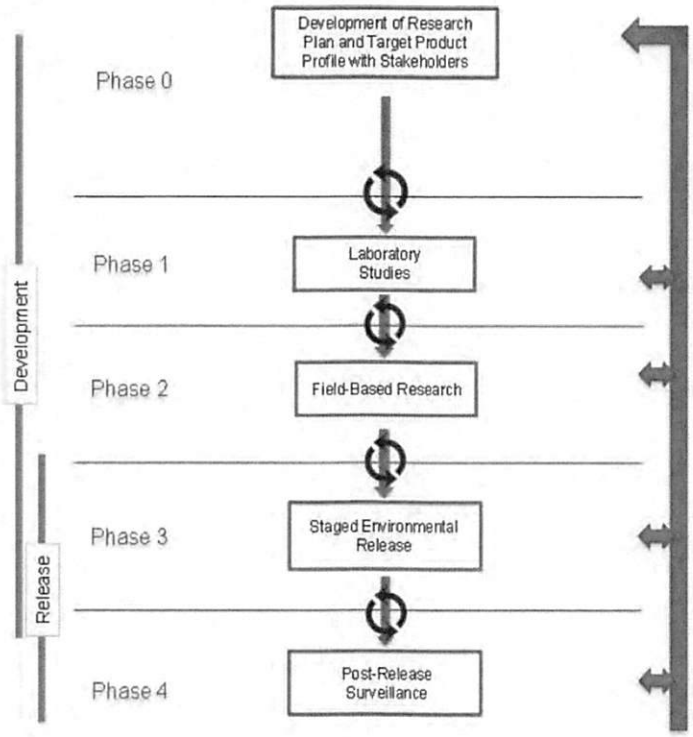
- Whenever possible, researchers should include a gene drive that spreads a visible marker to distinguish modified organisms and facilitate research and monitoring.

- Researchers, regulators, and other decision-makers should not rely upon a "reversal" gene drive as the sole strategy for mitigating the effects of another gene drive.

Integrating Science and Governance in Phased Testing



Risk assessment
Public engagement
Governance

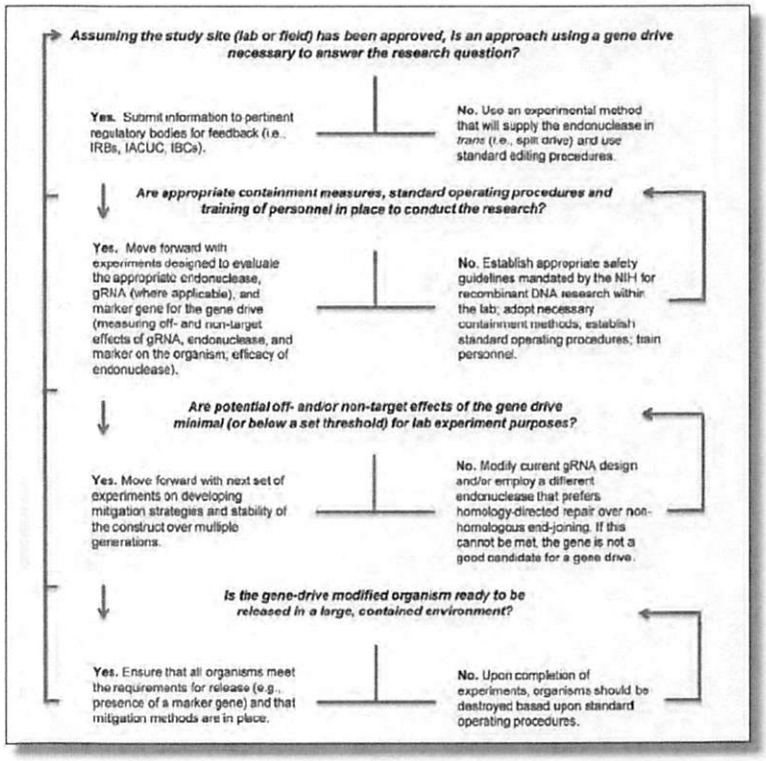


This stepwise, iterative approach to scientific evaluation should also identify and integrate social, environmental, regulatory, and ethical considerations .

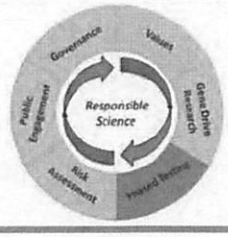
Results at each stage guide future research, and evidence-based decision making and governance.

Phased Testing Provides Evidence for Each Subsequent Decision

Each phase should include pre-defined "go/no-go" decisions for determining whether to move to the next phase, based on the scientific evidence, assessment of harms and benefits, efficacy, safety and regulatory preparedness.



Phased Testing: Selecting Sites for Field Tests



Criteria for site selection should include:

- Scientific and technical considerations (e.g., presence of the target species, methods for containment and confinement)
- Values of relevant publics
- Capabilities of local, regional, and national governance bodies
- Ability of researchers to engage with local communities

Recommendation: 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.

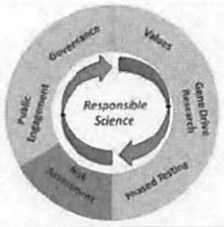
Reframing *Risk* and *Risk Assessment*

- *Risk* is commonly used to mean potential harm under conditions of uncertainty (e.g., "risk and benefit")

  However, *risk* itself is neutral – it means *probability* or *likelihood* under conditions of uncertainty (risk of harm, risk of benefit)

- *Risk assessment* is commonly used to mean evaluation of hazards and threats – especially in federal oversight
- The Committee called for broader-based assessment of risk as a multifactorial evaluation of potential benefit and harm.

From Environmental Assessment to Ecological Risk Assessment



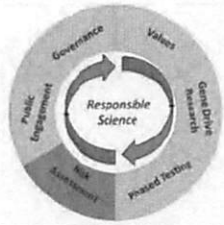
It is possible to estimate gene drives' risk using current approaches to *ecological risk assessment*

Advantages of ecological risk assessment:

- Quantify the probability of specific outcomes
- Trace cause-and-effect pathways
- Identify sources of uncertainty
- Incorporate concerns of relevant publics
- Compare benefits and harms
- Compare alternative strategies
- Inform research and public policy decisions

Relevant U.S. guidelines and technical documents are not yet sufficient on their own to guide ecological risk assessment for gene drive technology.

From Environmental Assessment to Ecological Risk Assessment



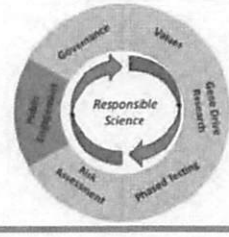
It is possible to estimate risk due to gene drives using current methodologies.

Advantages of ecological risk assessment:

- Quantify the probability of specific outcomes
- Trace cause-and-effect pathways
- Identify sources of uncertainty
- Incorporate concerns of relevant publics
- Compare benefits and harms
- Compare alternative strategies
- Inform research and public policy decisions

Relevant U.S. guidelines and technical documents are not yet sufficient on their own to guide ecological risk assessment for gene drive technology.

Public Engagement is needed in research, risk assessment, and governance

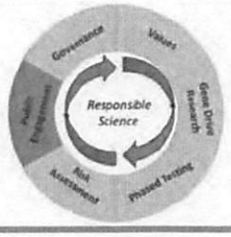


Public engagement cannot be an afterthought.

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.

Recommendation: Governing authorities, including research institutions, funders, and regulators, should 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.

Challenges in Public Engagement Call for Research into Best Practices



- What are the **goals** of engagement and how are they **prioritized**?
  - Incorporation of local knowledge and mutual learning
  - Transparency and building trust
  - Informed consent
- **When** should engagement occur?
- How can **cultural differences** be recognized and respected in ways that enhance deliberation?
- What are possible **triggers for polarization** and conflict? What steps lead to **consensus**?
- How should the **outcomes** of engagement **inform practice, decision making and governance** of research, development, and implementation?

Challenges to Governance of Gene Drive Research and Development (Part 1)

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.

Existing mechanisms of governance may be inadequate to address potential immediate and long-term environmental and public health consequences because they:

- Do not consider gene drives' intentional spread and potential irreversible effects on ecosystems
- Assume national and institutional capacity but lack clarity in their jurisdiction of oversight
- Provide insufficient structures for public engagement
- Do not address the potential for misuse
- Lack policies for collaborating with other countries with divergent systems

Challenges to Governance of Gene Drive Research and Development (Part 2)

The diversity of potential gene-drive modified organisms and contexts where they might be used reveals a number of overlaps and gaps in U.S. regulation.

- Is a gene drive inserted into a mouse a new animal drug (FDA), a rodenticide (EPA), or plant pest (USDA)?
- What are the responsibilities of U.S. agencies outside of the Coordinated Framework (e.g., U.S. Fish and Wildlife Service; Bureau of Land Management; National Park Service)?

Recommendation: The U.S. government should 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.

Challenges to Governance of Gene Drive Research and Development (Part 3a)

Multinational approaches to governance of gene drives will be required because a gene-drive modified organism knows no political boundaries.

Worldwide, most countries' regulation of genetically modified organisms is defined by the UN Convention on Biological Diversity (CBD) and its Cartagena and Nagoya Protocols.

- The U.S. is not a party to the CBD, but will need to participate in multinational approaches to governance of gene drives because a gene-drive modified organism will not respect political boundaries.

Challenges to Governance of Gene Drive Research and Development (Part 3b)

Regulation of genetically modified organisms under the U.S. Coordinated Framework and the CBD's Cartagena and Nagoya Protocols is predicated on containment. However, after release, a gene-drive modified organism is intended to spread.

NAS Recommendation: Research institutions, regulators, and funders should revisit international regulatory frameworks, national laws, non-government policy, and professional codes of conduct on research to determine whether and how they may be applied to specific contexts of gene drive research.

Since the NAS Report – Professional Statements

In August 2016, an ad hoc international group of prominent conservationists called for a **moratorium** on all gene drive research.

A Call for Conservation with a Conscience: No Place for Gene Drives in Conservation; http://www.synbiowatch.org/gene-drives-letter/

At its World Conservation Congress in September, the International Union for the Conservation of Nature (IUCN) called for ***assessment*** of gene drive research:

1 bis. CALLS UPON the Director General and Commissions with urgency to assess the implications of Gene Drives and related techniques and their potential impacts … in order to develop IUCN guidance on this topic, while refraining from supporting or endorsing research… into the use of gene drives for conservation or other purposes until this assessment has been undertaken; (ADOPTED)

095 - Development of IUCN policy on biodiversity conservation and synthetic biology
https://portals.iucn.org/congress/motion/095

Since the NAS Report – Funders' Statement of Principles

On December 1, 2017, the primary funders of gene drive research (FNIH, Gates Foundation, Wellcome Trust, Tata Trusts, and others) published a statement of principles based on the NAS report.

- Advance quality science to promote the public good
- Promote stewardship, safety and good governance
- Demonstrate transparency and accountability
- Engage thoughtfully with affected communities, stakeholders, and publics
- Foster opportunities to strengthen capacity and education

Emerson C, James S. Littler K, Randazzo F. Principles for gene drive research. Science 2017, 358 (6367, 1135-1136
http://science.sciencemag.org/content/358/6367/1135

Since the NAS Report – US Trials of GM Mosquitoes

In 2011, Intrexon (Oxitec) sought FDA approval for trials in Florida, classifying its Friendly™ *Aedes aegypti* mosquito as a *drug.*

- Evaluation under FDA rules allows a company to classify information from its application and FDA's evaluation as *confidential business information*
  - Oxitec did not keep its work confidential, and engaged in some public communication and engagement prior to a referendum in the Keys
  - On November 8, 2016, **58% of voters** in Monroe County, FL **favored** the proposed release in a non-binding referendum. In Key Haven, FL **~ 65% of voters opposed it.**
- In November 2016, the Florida Keys Mosquito Control Board approved Intrexon's proposed field trials
- In April 2017, the Board approved MosquitoMate's proposed field trials
- In October 2017, FDA transferred primary review to EPA's pesticide oversight

Since the NAS Report – Conference of Parties (COP) to the UN Convention on Biological Diversity

In December 2016, the Parties to the UN Convention on Biological Diversity (CBD) convened in Cancun, Mexico with gene drive research and "synthetic biology" on the agenda.

- Began to address gene drives in the Cartagena and Nagoya Protocols
- 160 organizations called for a moratorium on gene drive research
- Conference agreement approved on December 16, 2016 urged caution in field-testing the products of synthetic biology, including gene drives, and support for risk assessment of their potential effects
- Fall 2017 has seen controversy over DARPA's funding of gene drive research and involvement of CBD experts with DARPA's potential military application of "genetic extinction technology"
- The CBD's Ad Hoc Technical Group on Synthetic Biology met last week to plan the 2018 COP; report due in a few weeks

Take home points

- The ability to develop a gene drives with CRISPR/Cas9 is a remarkable, disruptive scientific achievement, that will remain controversial for the foreseeable future.

- Both enthusiasm for the significant potential benefits of gene drives and fear of their significant potential harms are based on theory and speculation, with still too little evidence.
  - The high stakes call for equally high standards of evidence and responsible science.
  - Responsible

Thank You!

Visit **nas-sites.org/gene-drives** to find:

- PDF of the report for free download
- Report in Brief (4-page lay summary)
- Briefing slides and archived webcast of public release