NOVEL AND EXCEPTIONAL TECHNOLOGY AND RESEARCH ADVISORY COMMITTEE

Minutes of Meeting

November 9–10, 2020

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH (NIH)
NOVEL AND EXCEPTIONAL TECHNOLOGY AND RESEARCH ADVISORY COMMITTEE (NExTRAC)
Minutes of Meeting
November 9–10, 2020

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NExTRAC is a federal advisory committee that provides recommendations to the NIH Director and serves as a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies. NExTRAC proceedings, reports, and links to meeting videocasts are posted on the website of the NIH Office of Science Policy to enhance their accessibility to the scientific and lay public.

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DAY 1

CALL TO ORDER AND WELCOME

Carrie Wolinetz, Ph.D., and Richard Whitley, M.D., NExTRAC Chair

Dr. Whitley called the meeting to order at 10:02 a.m. ET.

Dr. Wolinetz welcomed the committee members, invited speakers, NIH staff, and members of the public to the second meeting of the NExTRAC. The committee advises the NIH Director on and provides a public forum for scientific, safety, and ethical issues associated with emerging biotechnologies and their potential applications.

She announced that the two days would include a workshop focused on gene drive–modified organisms and the question of whether current biosafety guidance, regulatory frameworks, and conditions are adequate for NIH to consider supporting field release of such organisms. In addition, on the second day, a session would be devoted to a discussion about a draft report from the Working Group of the NExTRAC to Establish a Framework for the committee. Dr. Whitley indicated that the meeting agenda included time for public comments. In addition, several individuals provided written comments prior to the meeting and these comments were distributed to all NExTRAC members before the meeting.

CONFLICT OF INTEREST DISCLOSURES

Jessica Tucker, Ph.D., the NExTRAC Executive Secretary, reminded the committee members about the rules of conduct that apply to them as Special Government Employees, read into the record the conflict-of-interest (COI) statement, and indicated that related questions could be addressed to the Committee Management Office.

Dr. Tucker also announced that the meeting was open to the public and was being videocast and recorded. Presentations will be posted to the NExTRAC website.

GENE DRIVE WORKSHOP

This workshop included a review of the charge to the Gene Drives in Biomedical Research Working Group, along with an overview of gene drive technologies and their applications. The working group's roster is available online.

GENE DRIVES: BIOSAFETY GUIDANCE AND CONDITIONS FOR FIELD RELEASE RESEARCH

Overview of Charge to the Gene Drives in Biomedical Research Working Group

Zach Adelman, Ph.D., and Cinnamon Bloss, Ph.D., Gene Drives Working Group Co-chairs

Dr. Bloss and Dr. Adelman are the co-chairs of the working group, which was charged with the following:

1. Consider whether existing biosafety guidance is adequate for contained laboratory research utilizing gene drive technology.
2. Outline conditions (if any) under which NIH could consider supporting field release of gene drive–modified organisms.

The working group includes seven NExTRAC members (the two co-chairs and five other members) and four *ad hoc* members. One *ad hoc* member is with NIH, and the others were involved in the creation of a 2016 report, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values,* published by the National Academies of Sciences, Engineering, and Medicine (NASEM). [Within these meeting minutes, the report is referred to as the NASEM report.]

The working group has met one or two times per month since February 2020 to learn about and discuss the current status of regulatory oversight, biological and environmental risk assessment, risk mitigation, the NASEM report, and strategies for public engagement. Dr. Adelman said that over the past several months, the working group had opportunities to learn from subject matter experts and gathered and examined guidance issued by NIH and for-profit and nonprofit organizations.

Dr. Bloss said that the group also considered how to provide advice on the adequacy of the current landscape of biosafety guidance for contained research, as well as the knowledge and conditions that need to be in place to help ensure that field release studies could be conducted safely and ethically.

Dr. Adelman said that he and Dr. Bloss would like to emphasize that the working group is in a listening mode now that they have identified the most relevant questions for eliciting opinions and input related to gene drive research. Input and feedback regarding these questions and other issues will serve as a framework for discussion by the working group over the next few months as the working group prepares a draft report for the NExTRAC's consideration in mid-2021.

SESSION I: GENE DRIVES IN BIOMEDICAL RESEARCH

Overview of Gene Drive Technologies and Applications

Anthony James, Ph.D.

Dr. James explained that a gene drive is fundamentally an inheritance bias for a specific genotype. Through this process of inheritance, a gene is guaranteed to pass from one

generation to the next and, ultimately, throughout a population. The engineered genes are inherited in a manner that does not conform to expected Mendelian ratios, such that a trait can spread through a population even if it does not benefit the individual organism. Gene drives are more common among diploid organisms during sexual reproduction, although exceptions exist.

Dr. James explained that a *drive mechanism* is the underlying biological drive feature that gives rise to a *drive system*, which is the final synthetic product that achieves the inheritance bias. Several gene drive mechanisms exist, such as competitive displacement and reduced heterozygous fitness—genetic phenomena based on chromosome mechanics. An example of an underdominant system is one in which two gene suppressors can turn each other off; if both suppressors are in a cell, the cell survives, but if only one is present, promoter release stimulates the production of a lethal effector molecule, causing cell death. A second example, originally described in Drosophilia, is a meiotic drive also know as segregation distorters. A third mechanism is gene conversion, first described in yeast, that results from DNA break and repair mechanisms. There are also gene drive mechanisms based upon infectious and infectous-like agents. Examples of these agents are extracellular and intracellular symbiotic microorgansims, cytoplasmic incompatibility (*Wolbachia* species for example), paratransgenesis, and transposons. Also based on underdominance are drive systems that rely on hybrid sterility. Other gene drive mechanisms include meiotic drives—also called segregation distorters—and gene conversion based on DNA-break-induced repair, mediated by nucleases, such as Cas9.[1]

Dr. James outlined several useful concepts, including the following:

- Endogenous genetic or epigenetic elements originate from the wild type of the species of interest
- Exogeneous elements not originating from or common to the wild type is a concept that can be thought of as the introduction of foreign DNA
- Vertical transmission of the element is the passage from parent to progeny, usually via either germ cells or fomites
- Horizontal transmission is the transfer of a genetic element from one type of organism to another, either members of the same or different species

In addition to gene conversion systems, other gene drive systems are available, including autonomous (or autocatalytic) systems that carry all the genetic information needed to move themselves through a population by causing an inheritance bias coupled in a cis configuration as part of a single construct. These drives involve introducing a gene or sequence that includes Cas9 nuclease, which induces a double-stranded break in DNA, and a guide RNA for continuous mobility of the nucleotide-protein complex in a population.

Split systems (based on either physical or temporal separation) function only when all the components exist in the same cell. Therefore, a process is needed to bring the components together to function as a drive. Examples include daisy chain systems.

[1] Gantz VM, Bier E. Genome editing. The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations. *Science,* 2015;348(6233):442-444. doi:10.1126/science.aaa5945

Another type of drive relies on low- or no-threshold dynamics that involve single releases of small numbers of gene drive organisms, resulting in every organism in the population carrying the drive system. Other drive systems have high-threshold dynamics. In this case, gene drives are released at baseline at or above a minimal frequency in relation to the target population.

In addition, some systems are designed to be nonlimiting, with an expectation that the system will persist in the environment. In contrast, self-limiting systems have design features that cause the systems to be lost from the population eventually.

A gene drive can introduce favorable traits into populations, or the technology can suppress or replace populations, primarily of organisms with short lifecycles.

Dr. James outlined several examples of possible environmental and agricultural benefits of gene drives. In terms of public health benefits, Dr. James spoke of using gene drives to eliminate the insect vectors of malaria, dengue fever, chikungunya virus, Zika virus, and Lyme disease or to attack pathogens, such as the parasites that cause schistosomiasis or the snails that carry the parasites. Another possibility is humanizing experimental and donor animals for fundamental research that may lead to translational advances.

Gene drive technology comes with several challenges, such as potential regional and global impacts, potential problems of off-target effects, and unexpected adverse consequences of drive or cargo failures. The concerns that science and society are facing include the need to consider local, national, and international regulatory realms and issues related to moving from individual-level to community consent for gene drive applications.

Dr. James listed four classes of confinement strategies that could serve as safeguards for gene drive experiments in the laboratory:[2]

- Molecular confinement, such as split-drive technology, in which the Cas9 component and the guide RNA are in separate loci
- Ecological confinement based on performing experiments outside the habitable range of the organism or in an area without wild mates (e.g., performing experiments with *Anopheles* mosquitoes in Boston)
- Reproductive confinement, which involves using a laboratory strain that cannot reproduce with wild organisms
- Barrier confinement, which involves the use of physical barriers between organisms and the environment

In closing, Dr. James offered some recommendations for the NExTRAC to consider as it develops a framework for gene drive research:

[2] Akbari OS, Bellen HJ, Bier E, et al. BIOSAFETY. Safeguarding gene drive experiments in the laboratory. *Science,* 2015;349(6251):927-929. doi:10.1126/science.aac7932

- *Review and reconcile past efforts.* The NExTRAC should review and integrate guidance and recommendations from existing guidelines, the NASEM report, and community-generated documents.
- *Strive for consensus.* Adopt unified language in the framework to facilitate adoption of guidelines.
- *Develop guidelines that are sufficiently broad.* No one-size-fits-all solution exists, because of organisms' genetic plasticity, differing dispersal qualities, and varying reproductive capacities. Any general guidelines should be broad enough that they can be interpreted for the number and variety of organisms being considered for field trials.
- *Consider biology, not labels.* When developing regulations, avoid relying on simplistic classifications.
- *Use precise language.* Avoid jargon and catchphrases.
- *Do not over-regulate.* Consider what has happened in other fields. Revising established regulations is difficult. Other fields have been hampered by regulations that were too restrictive. Guidance and principles are easier to revise.
- *Remember that lack of knowledge is never an answer to solving complex problems.* Unknowns are exciting for scientists, but researchers need to answer questions about conducting research safely, to allay some concerns of the public.

General Discussion

Referring to the second part of the charge to the working group, Mildred Cho, Ph.D., asked about field release and the risk of gene flow from gene drive–modified organisms to wild populations. Dr. James spoke about an initiative taking place at the University of California, Irvine, that is exploring the possibility of moving mosquitoes from the laboratory to the field. The research team came up with criteria for maximizing the safety of this research. The team developed a set of criteria for an ideal site for a first-release experiment. This group sought out islands that were physically, geographically, and genetically isolated. The team then collected mosquitoes and compared them with populations on other islands and the mainland to look at gene flow between the populations. The results are pending.

Kenneth Oye, Ph.D., commented on the need for more knowledge about molecular containment, especially whether thresholds or split drives work. As the NExTRAC gets closer to developing guidelines for field release, it will be important to understand how to test the effectiveness of these safeguards prior to field testing. It is a chicken-or-egg problem: How can scientists understand the efficiency of gene transfer and the consequences of release without field studies? Dr. James said that the World Health Organization (WHO) and other entities suggest a phased approach. The first phase would entail increasing the size of cages in the laboratory, followed by cage studies in the field, and then field-release studies. A great deal of field work is necessary to (1) demonstrate that no significant gene flow occurs in a geographic space and (2) put a functional mitigation strategy in place to eliminate released organisms should an unexpected event occur. For example, insecticide application could eradicate drive-modified mosquitoes, but it is necessary to ensure beforehand that the target mosquitoes are susceptible. For other organisms, secondary genetic mechanisms might serve as mitigation strategies,

although Dr. James advised against relying on a genetic means to rectify a genetic problem.

SESSION II: BIOSAFETY GUIDANCE FOR CONTAINED RESEARCH

Panel Discussion

Moderator: Zach Adelman, Ph.D.

Panel Members: Lyric Bartholomay, Ph.D.; David Gillum, M.S., RBP; Kathryn Harris, Ph.D., RBP; and Ruth Müller, Ph.D.

The panel members delivered brief presentations in response to the following questions:

- Is current physical containment guidance adequate to address contained research with organisms containing gene drives?
- Would additional guidance for certain species be useful?
- Are existing general principles for biosafety risk assessment and management adequate for contained gene drive research? What additional guidance might be useful?

Overview: biosafety guidance pertaining to contained research. Dr. Harris is the Senior Outreach and Education Specialist in the NIH Office of Science Policy (OSP). She presented information relevant to gene drive research in laboratory settings, starting with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*). The *NIH Guidelines* are updated periodically; the latest version was released in April 2019. The document is not intended to be a regulatory document, nor does it provide information specific to gene drive–modified organisms, though it does pertain to much research involving gene drives. It covers specific practices for constructing and handling recombinant or synthetic nucleic acid molecules for contained research. All research conducted at an institution that receives any NIH funding for recombinant or synthetic nucleic acid research is bound by the *NIH Guidelines*. Also, other federal agencies and some private funders require adherence to the *NIH Guidelines* as a term and condition of funding.

The *NIH Guidelines* require that institutions establish Institutional Biosafety Committees (IBCs) to review certain types of research involving recombinant or synthetic nucleic acids. The vast majority of research that is not exempt from the *NIH Guidelines* falls under Section III-D. Research that falls under Section III-D requires IBC approval before initiation. A category of research that is pertinent to gene drive work involves whole animals and is work covered under Section III-D-4. This line of work includes the generation of a transgenic animal or the testing of recombinant or synthetic nucleic acids. Certain types of research require both the approval of the NIH Director or others at NIH and IBC approval.

The *NIH Guidelines* also apply to biological practices for containment, survival, and transmission of recombinant or synthetic organisms. Section III-E-3 of the *NIH Guidelines* pertains to experiments that involve the generation of transgenic rodents. Regarding physical containment, Dr. Harris explained that four biosafety levels (BL1

through BL4, with BL4 being the most restrictive) pertain to work practices, safety equipment, and facilities.

The Centers for Disease Control and Prevention's *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) is essentially a code of practice for the safe conduct of work in laboratories, from a biosafety perspective; it is not a regulatory document. The document contains several sections relevant to emerging technologies. The sixth edition is about to come out.

Biosafety guidance for contained research with arthropod vector species. Dr. Bartholomay, at the University of Wisconsin-Madison, said that the *NIH Guidelines*, BMBL, and Arthropod Containment Guidelines (ACG), revised in March 2019, are the main standards pertaining to recombinant DNA experiments. With regard to transgenic organisms, the ACG covers phenotypic changes resulting from genetic modifications, not ecological and environmental issues.

Working with IBCs can also help maximize the safety of personnel, other building occupants, the community, and the region. Dr. Bartholomay's laboratory at the University of Wisconsin–Madison is an environmentally controlled space where insects are housed in small screened cages. Safety provisions include physical barriers, limited access, signage, containment systems, and systems for detecting insect escapees, including sentinel traps. Vector rooms are located behind sealed doors and away from common corridors. White surfaces make it easier to spot escapees. It is also important to use safety reminder signage and reduce clutter in the lab. Personnel work with insects in screened areas separated with plastic strips to knock any insects off people as they leave a workspace. Dr. Bartholomay expects that the setup for ongoing vector work is likely designed to adapt to containment needed for gene drive experiments.

Dr. Bartholomay emphasized that transgenic mosquito research is critical to protecting human health and said that a solid foundation of guidance exists for risk mitigation for contained research in the laboratory and the field.

Biosafety guidance for contained research with gene drive–modified organisms: A biosafety officer's perspective. Mr. Gillum outlined roles in assessing the risks of gene drive research. Principal Investigators bear the primary responsibility for understanding and assessing the risks of their own work, including with gene drives. Biosafety officers (BSOs) and IBCs work together to review the proposed research, assess risks, and determine appropriate containment facilities and risk mitigation strategies.

In terms of nomenclature, Mr. Gillum distinguished between the terms *confinement* and *containment*:

- *Confinement* refers to the use of ecological conditions or biological methods to prevent persistence of an organism in the environment. An example is climatic isolation, when the regional climate or season would not allow the transgenic organism to survive where it is released.

- *Containment* is the use of human-made or natural physical restrictions to prevent unintended or uncontrolled release of an organism into the environment. Examples include cages and geographically isolated locations, such as islands.

In general, BSOs and IBCs understand and have extensive experience in physical containment (i.e., barrier confinement) principles and practices. Most BSOs consider barrier confinement to mean physical containment in normal biosafety practice.

The expertise level and quality of IBCs and BSOs vary from one institution to another, and many institutions do not have a BSO at all. Mr. Gillum suggested creating a requirement for institutions—including community colleges—to have a BSO on the IBC if they are conducing gene drive research. There are more than 1,000 BSOs around the world.

BSOs are not required to have an understanding of genetics and molecular biology, although that knowledge would be helpful for gene drive research. A recently published study found that few BSOs felt confident in their ability to assess the risk of gene drive–modified organisms.[3]

Mr. Gillum highlighted several sources available to equip BSOs with the expertise they need for risk assessments of gene drive research.[4] The American Biological Safety Association (ABSA) has hosted webinars featuring subject matter experts who explain the science of gene drives. Mr. Gillum organized a gene drive course in 2015 and an ABSA conference on the subject each year thereafter. Additional courses are offered during the conferences. Other biosafety associations exist around the world.

Under the *NIH Guidelines*, it is clear that principal investigators bear the primary responsibility for understanding all aspects of their research, including the safety and risks of their own work. However, many investigators, BSOs, and IBCs do not fully understand biological (i.e., molecular, ecological, and reproductive) containment in the context of gene drives. This presents challenges in conducting risk assessments when biosafety experience has been largely limited to physical containment. In addition, some transgenic organisms have dual-use potential that should be accounted for in risk assessments.

Mr. Gillum offered several recommendations for the NExTRAC to consider:

- Provide guidance on the organisms most often used in gene drive experiments, as well as experiments in species that pose the highest risk to society and the environment.
- Address the need for training and educational opportunities for BSOs and IBCs. NIH could partner with ABSA and other organizations to develop and provide gene drive training.

[3] O'Brochta DA, Tonui WK, Dass B, James S. A cross-sectional survey of biosafety professionals regarding genetically modified insects. *Appl Biosaf*, 2020;25(1):19-27. doi:10.1177/1535676019888047
[4] Krishnan, P. and D. Gillum. "Gene Drive 101: a basic guidance resource for biosafety professionals." *Applied Biosafety* 22.4 (2017): 181-184.

- Establish a forum for communities of practitioners to come together to share knowledge and experiences pertaining to gene drives.
- Consider incorporating the ACG into the *NIH Guidelines*. Existing guidance is adequate for barrier confinement for gene drive research, but there is a lack of guidance on risk assessment for biological containment methods.
- Provide guidance for species other than arthropods.
- Develop standard risk assessment tools for use by BSOs. Such tools could help BSOs understand that lower physical containment levels may be supported when molecular strategies for containment are employed.
- Provide a consensus scientific document to help with the determination and management of the risks associated with gene drives.
- Develop tools for conducting risk assessment.
- Collaborate with the do-it-yourself (DIY) community.

By challenging traditional assumptions about how science works and who is responsible for governance, it should be possible to create a governance model that works for all.

Contained Insectary of PoloGGB, Terni, Italy. Dr. Müller described the insectary facilities, highlighted some regulatory aspects of gene drive research, provided an overview of the mosquito repository, and presented photographs and floor plans of the facility in Terni, which hosts a laboratory for ecological and genetic studies of malaria vectors. The facility supports arthropod containment level 2+ (ACL-2+) research and is designed to support ecological experiments with gene drive–modified mosquitoes.

The facility has two breeding rooms, as well as three large cage chambers, a small molecular lab for barcoding mosquitoes, and a microscopy laboratory. Aside from physical containment, safety measures include ecological containment through the use of mosquitoes that are not present in Europe. Dr. Müller said that perhaps the most important aspects of the containment are the standard operating procedures (SOPs) and well-trained staff.

The research is subject to international law (The Cartagena Protocol on Biosafety), European law, and Italian law. The program receives authorization from Italy's Ministry of Health to operate at ACL-2 and BSL2 and to import African wild-type mosquito colonies. In addition, the program obtained an official opinion from the Istituto Superiore per la Protezione e la Ricerca Ambientale. The scientists also follow the directive on the deliberate release of genetically modified organisms into the environment and protection of works from exposure to biologic agents.

The program is audited three or four times per year. The insectary's biosafety group consists of experts on biosafety, communications, engineering, vector biology ecology, and vector control.

In terms of biological containment, the PoloGGB scientists use self-limiting gene drives and female fertility-suppressing drives, among others. The scientists also monitor for development of resistance. Large cages enable experiments under tropical conditions and

natural conditions. Technicians provide blood meals though sealed openings. Modified insects are released into the large cages at a low initial frequency.

PoloGGB produces data for regulators and works with the Target Malaria project on malaria research and training in Mali, Burkina Faso, and Uganda. Stakeholders are welcome to submit dossiers.

General Discussion
On the topic of audits to ensure that safeguards are adequate, Dr. Müller said that her facility undergoes regular audits that are conducted by external experts who work on a contractual basis, but the research team set up the IBC at their institution.

Could community risk assessments be published and shared? It was noted that publication through NIH or ABSA might be possible, but institutions are concerned that the assessments could be misconstrued or lead to lawsuits. Those concerns are barriers to publishing risk assessments.

In response to a question about the adequacy of the ACG, Dr. Bartholomay said that they are broadly understood to be helpful, but problems have arisen when IBCs consider the ACG as required policy rather than guidance. It had been challenging for junior investigators to get their laboratories approved by the IBC because of limited resources. Similar problems arise for out-of-country laboratories. When the ACG was updated, the authors clarified that risk assessment is a foundation for safe research, but the assessment must take context and resources into account.

Jason Delborne, Ph.D., asked about failure rates of arthropod containment facilities and noted a need for catastrophe planning because gene drives can perpetuate. Dr. Müller said that European authorities required consideration of worst-case scenarios, such as a major break in a large cage or earthquakes. She worked with experts to develop worst-case scenarios and plan mitigation strategies, which depend on the organisms and the laboratory's location and size. Key aspects of planning include inspections, validation of the facility design, geography, and infrastructure. The committee also discussed other factors related to the transgenic organisms that should be taken into account during planning, such as the type of drive, the likelihood of a worst-case scenario, and methods for confining or terminating the strains. Insofar as which regulatory agencies might be involved in planning for worst-case scenarios, many agencies might be involved in the United States. Dr. Müller underscored the need for transparency about research activities and said that she consulted with the Ministry of Health as the main contact but also informed the Ministry of the Environment.

Dr. Müller said that operational costs include those for trained staff, safety engineering, public engagement, and communications. For infrastructure, costs include maintenance of contracts, the need for system redundancy, and regular molecular confirmation of experimental strains. Most costs are in line with those for other types of vector research.

The NExTRAC discussed the role of IBCs and some members noted that IBCs should think beyond barrier confinement strategies as they conduct risk assessments and that they consider molecular, ecological, and reproductive strategies as well. IBCs are knowledgeable about pathogen confinement, but they have less familiarity with confinement mechanisms and the types of experiments needed for risk assessments for transgenic organisms. Regarding the composition of IBCs, the *NIH Guidelines* specify the types of expertise required, which depend on the type of research. Gene drive expertise is not specifically required on IBCs, but there is an expectation that IBCs have the expertise to review the work being done at their institutions.

In terms of guidance for risk assessment, NIH has issued guidance on lentiviral vector risk assessments, for example. As another example, there is other NIH guidance that applies to research with high-pathogenicity influenza strains.

Freda Lewis-Hall, M.D., asked Mr. Gillum whether he was referring to risk assessment using Bayesian networks to find relationships between hazards and their networks. Mr. Gillum provided several examples of the safeguards and types of risk assessments needed. For a molecular confinement strategy, the plan should describe how well it will work and whether it can be combined with other confinement strategies, such as ecological confinement, including seasonality. For a reproductive confinement strategy, the risk assessment plan should describe characteristics of the transgenic organism that would preclude it from mating with wild organisms. Mr. Gillum spoke about the need for multiple examples of possible experiments with different species using different confinement strategies to consider whether the work could be done in a BSL2 lab instead of a BSL3 lab, for example. Dr. Lewis-Hall followed up, saying that a compilation of existing assessments of confinement strategies would provide a foundational framework so it would not be necessary to start from scratch every time.

Dr. Harris underscored the importance of understanding the state of knowledge about biological confinement strategies; without testing strategies in the wild, there is a degree of uncertainty inherent in risk assessment, limiting the information that researchers can provide to IBCs. Modeling gives some indication of the risk and efficacy of confinement strategies, but the lack of data based on testing in the wild is limiting.

With regard to the principle of uncertainty in risk assessment, Dr. Bartholomay described risk assessment for experiments involving chimeric viruses. The wild-type vector normally necessitates operating at BSL2, but as an added safeguard, the work with the chimeric strain was elevated to BSL3. As part of the risk assessment, field-caught wild mosquitoes were quarantined to ensure they were not carrying pathogens and then brought into production as a way of assessing confinement strategies. To address concerns about possible escape from the laboratory into the building, procedures are in place for shutting down the laboratory and fumigating to prevent escape.

Dr. Müller explained that the facility where she works was designed specifically for gene drive research. Every procedure was tested, including measurements of DNA release into

the wastewater stream. Experiments help reduce the uncertainty around scenarios in which the transgenic organisms were introduced into a wild-type background.

Dr. Oye observed that the extent to which risks are correlated would affect risk assessment, because multiplicative approaches would not suffice. One would have to evaluate the probability of failure at each level and identify unknowns. Mr. Gillum said that risks are correlated and additive. More research is needed on reproductive confinement strategies to understand the risks. Dr. Oye suggested that the NExTRAC take uncertainty into account during deliberations. Dr. Cho said that thinking about how to aggregate the risks, whether additive or multiplicative, may not be as important, but confinement approaches and risk strategies should be considered as layers that should be better understood in a qualitative way. Having multiple confinement strategies in place would be powerful.

Dr. Adelman said that humans will be the weak link in terms of containment. He asked how the panel members train personnel and assess adherence to procedures. Dr. Müller said that staff are key. Scientists are trained on SOPs and required to follow strict rules. In addition, at her facility, a journal club reinforces their knowledge of procedures. The BSO assesses compliance with SOPs, communicates with the relevant ministries, addresses any external inquiries, and is responsible for maintaining the infrastructure.

Kathleen Boris-Lawrie, Ph.D., said that BSOs and IBCs are often more aware of BSLs for lentiviral vectors than for arthropods. Arthropod safeguards may entail extreme measures, such as requiring that personnel wear heavy protective gear while dissecting mosquitoes.

Dr. Harris said that OSP is available to guide and advise IBCs and BSOs. Because many institutions have worked with agricultural research entities, those institutions have gained substantial experience and expertise on confinement strategies and risk assessment.

SESSION III: THE SCIENCE OF BIOLOGICAL AND ENVIRONMENTAL RISK MITIGATION

Panel Discussion

Moderator: Kathleen Boris-Lawrie, Ph.D.

Panel Members: Omar Akbari, Ph.D.; Fred Gould, Ph.D.; Antoinette Piaggio, Ph.D.; and Phil Messer, Ph.D.

The session covered current scientific approaches, application to different species, and knowledge gaps pertaining to biological and environmental risk mitigation for gene drives, whether for contained research or field release. Three questions formed the basis for discussion:

- What are the current state-of-the-art strategies for biological risk mitigation?
- What are current environmental risk mitigation approaches for different species?
- Are adequate biological and environmental strategies available for risk mitigation? What additional knowledge would be useful?

Science of biological and environmental risk mitigation approaches. Dr. Piaggio said that the mission of the National Wildlife Research Center of the U.S. Department of Agriculture (USDA) is to apply scientific expertise to resolve human–wildlife conflicts while maintaining the quality of environments shared with wildlife. She is interested in using synthetic biology instead of toxicants as a way to control invasive organisms to help maintain environmental quality.

Dr. Piaggio outlined a set of core commitments for field trials of gene drive organisms. These commitments build on the principles of engagement, scientific integrity, and public transparency: (1) fair partnership and transparency; (2) regulatory evaluation and risk–benefit assessment; (3) product safety and efficacy, based on acceptable performance parameters; and (4) monitoring and mitigation plans, developed in concert with experts and stakeholders.

Locally fixed alleles (also called private alleles) are a novel means for localizing drives to an island population that is genetically isolated from neighboring populations. This approach involves targeting one or more locally fixed alleles as the target for a gene drive. Dr. Piaggio collaborated on a modeling study showing that escape of the drive to a neighboring population in which the target allele is not fixed might lead to little, if any, transient suppression of the non-target population. In addition, selection would make resistant organisms more fit.[5]

Dr. Piaggio was involved in a field study comparing mouse populations on several islands and in neighboring mainland areas. Measures of heterozygosity (using whole genome data) demonstrated substantially less diversity on the islands than on the mainland. The investigators identified 40 fixed-allele candidates in the island populations that could be drive targets.

Dr. Piaggio mentioned various confinement approaches for safeguarding gene drive experiments in the laboratory. In the field, several approaches could limit spread of the gene drive–modified organisms into nontarget populations, including careful site selection and spatial limitation of the gene drive by exploiting locally fixed alleles. Population genomics studies would be key to identifying candidate private alleles.

More work remains to develop strategies to minimize risk of spread of drives outside of the target population before field trials take place. Substantial information must underlie risk mitigation strategies. It can take years to characterize the population genetics of a target population (e.g., subspecies, levels of genetic diversity, genetic connectivity), but these data are the key to minimizing the risk of spread. Also, the lack of knowledge about the basic biology of target systems (e.g., mouse breeding ecology) is a critical gap that can take years to fill. Despite the challenges, Dr. Piaggio considers synthetic gene drives as a future effective and humane method for suppressing populations of invasive rodents. She suggested that gene drives also pose less of an environmental burden than toxicants.

[5] Sudweeks J, Hollingsworth B, Blondel DV, et al. Locally fixed alleles: A method to localize gene drive to island populations. *Sci Rep*, 2019;9(1):15821. doi:10.1038/s41598-019-51994-0

State-of-the-art strategies for gene drives and biological risk mitigation. Dr. Akbari noted that gene drive technology is not a new field, but CRISPR Cas9 technology has accelerated and democratized this approach. Nonlocalized drive systems are self-propagated and predicted to spread beyond the release site. In contrast, localized drive systems generally have high thresholds and will spread only if introduced above a certain threshold. Self-limiting drives, such as split homing drives, are time-limited; they do not persist in the population. Gene drives could have roles in suppressing or modifying populations.

Non-localized linked homing drives could be used for population modification or suppression. With a threshold-independent drive system that self-propogates, the organism will spread throughout the population, and since these systems are nonlocalized, they could also spread to neighboring populations. Threshold-independent suppression transgenes could drive a population into extinction. Neither of these approaches can be reversed except by releasing an alternative system or reversal gene drives, but that would raise questions about the wisdom and acceptability of releasing another genetically engineered system.

One approach to limit gene drive spread would be to target a private allele that is exclusive to an isolated population. Releasing the drive organism on a limited-access, ecologically isolated island would minimize risk, but a mitigation strategy would need to be identified in case of spread to other areas via aircraft, ships, winds, or currents. There is also a concern about populations developing resistance to the drive.

Localized gene drives have been developed that could also be used for population modification or suppression. These high threshold or self-limiting drives have the advantages of being controllable, inherently confinable, reversible, safe and effective. High threshold drives require release of organisms above a threshold in order to be able to spread. Self-limiting drives, such as split homing drives, which remove the Cas9 nuclease from the drive element, will not persist or spread past the release site. Such systems have been built and tested in flies, mice, and mosquitoes. Dr. Akbari described an *A. aegypti* split homing drive that is self-limiting and could be confinable based on modeling simulations.

Dr. Akbari suggested that confinable split homing drives might be the optimal choice for the first field trial of gene drive modified organisms.

Not all gene drives are created equal. The focus of Dr. Gould's presentation was on gene drives based on underdominance and on tethered homing (with underdominance). Underdominance and tethered homing gene drives have thresholds of at least 27%. Neither is temporally limited, and both are spatially limited. Drive resistance is a possibility with both of these technologies.

With overdominance, the heterozygote has more fitness than the homozygotes. With underdominance, the heterozygote is less fit. People have been thinking about

underdominance for strain replacement since the 1940s, but efforts were constrained by a lack of tools for creating underdominant strains.

The goal of an underdominance-based drive is to change a population, not eliminate it. If underdominance is used as a gene drive, a local population can be transformed when transgenic individuals are introduced at a level exceeding 25%. Then, as the transgenic individuals migrate into nontarget populations, they disperse and become outnumbered, so they do not persist.

The Target Malaria project recommends phased gene drive trials:

- Phase 1: Release of sterile male mosquitoes so that mating with wild females would not result in offspring.
- Phase 2: Release of a self-limiting male bias strain; mating with wild females would result in primarily male progeny. This phase would not involve a gene drive. The modification would be passed on for a limited number of generations.
- Phase 3: Self-sustaining approaches, in which modified mosquitoes are fertile and could pass on genes that would spread through the mosquito population, resulting in either a male bias sex ratio or infertile females.

Some challenges are associated with different types of drives. For example, populations might develop resistance to suppresion drives, while for replacement drives, the target pathogen might adapt, or a breakdown in the genetic sequence could occur.

Prospects and limitations of modeling in the assessment of gene drive systems. According to Dr. Messer, risk assessment often depends on modeling analyses to make qualitative predictions about the outcome of a drive release, as well as quantitative predictions about the dynamics of a drive. What are the prospects and limitations of modeling in the assessment of gene drive systems? Modeling provides some insights into the expected behavior of a gene drive before any real-world application occurs. To support accurate predictions, some level of biological realism needs to be included in models. Key biological parameters include genetic complexity (e.g., the fitness cost of the drive), demographic complexity (based on the lifecycle of the population, including discrete and overlapping generations), and ecological complexity (e.g., seasonal variations, migration patterns).

Dr. Messer offered a few examples to demonstrate the effect of incorporating different levels of realism in a model on the model's outcome. In terms of genetic complexity, guide RNA multiplexing can make homing gene drives more efficient. If a drive targeted multiple sites, it could succeed at each of the sites; even if resistance developed at one site, another site would still work. A very simple model would indicate that more sites would yield greater drive conversion efficiency. However, it turns out that there is an optimal number of guide RNAs; if more sites are included, the drive becomes less efficient. Therefore, the best approach is to model less biological complexity but in a more realistic way. Other examples showed the effect of modeling assumptions about demographic and ecological complexity.

In closing, Dr. Messer underscored the important role of modeling in predictions of risk and benefit and in the process of identifying which technologies might work better in certain circumstances. Modeling assumptions regarding genetic and demographic parameters could change the expected outcome in fundamental ways, so questions arise about key concepts, such as the notion of a comfortable gene growth strategy. Investigators will have to deal with the challenge of limited experience to judge the appropriateness of models and gauge the accuracy of predictions. Experimental verification will remain critically important.

General Discussion

Before the panel discussion began, Dr. Boris-Lawrie suggested thinking about drive spread in the same way as pathogen spread in terms of risk mitigation strategies. Dr. Akbari recommended discussing effector genes. Although good ones exist for *Plasmodium falciparum,* dengue fever, and Zika virus, for example, testing has been limited to laboratory strains. Efficacy should be investigated in field-caught mosquitoes, as is being done in a mobile lab in Africa.

Dr. James Collins indicated that the hardest part of this endeavor may lie in capturing ecological complexity in models and experiments, especially with regard to refugia in the environment. Dr. Piaggio made the point that ecological challenges occur with most control strategies (including gene drives) and noted the importance of phased field trials to address some of these questions. Dr. Gould noted that we should learn from the *Wolbachia* releases ongoing now, to consider what is the same and what is different. NExTRAC members discussed the need for more information and detailed modeling to understand potential benefits and risks of field-release studies. NIH has had a key role in funding population ecology studies regarding *Aedes* mosquitoes.

There was discussion about the goal of a gene drive approach, and how it should be considered when risk mitigation strategies are being assessed. If the aim is to introduce an allele into a population, then the limiting threshold is central in decision making. Knowledge of ecological complexity is more important for suppression drives confined to a spatial area. It was expressed that it would be essential to be very sure about ecological parameters, such as the degree to which an island is isolated in terms of migration patterns, and that entails significant research beforehand. Ecology and biology are both challenging in terms of control strategies, especially strategies based on toxicants. For example, mice have breeding strategies that can vary seasonally. Years of work would be necessary to learn how the breeding system works. Dr. Piaggio noted that structured trials, as recommended in the NASEM report, would provide a logical progression for field-release trials.

NExTRAC members discussed the lack of knowledge about the effectiveness of safeguards for field release. Dr Oye asked, how can the effectiveness of designs intended to be localized or limited be tested before field release? Also, safeguards would probably influence the effectiveness of gene drives, introducing a source of uncertainty that would vary from application to application.

In addition, members discussed how potential benefits should be weighed when considering these decisions. Malaria, for example, kills many people, especially children, every year; eradicating *Anopheles* mosquitoes would save lives. Potential benefit should factor into decision making and regulations, although not all regulators allow risk assessments to consider possible benefit.

Dr. Gould noted that if a drive fails, biological consequences would likely result. For example, dengue might be suppressed in a region for a time, but that could result in loss of herd immunity in the human population. Regarding *Wolbachia* and replacement drives, he noted it might be advisable to have standards that differ from those for transgenic organisms.

With regard to developing standards for risk mitigation, the NExTRAC members reflected on the charge to this committee and discussed standards that might account for diversity and complexity. An important first step, as noted by Dr. Boris-Lawrie, would be identifying knowledge gaps to help focus the committee's lens. Dr. Akbari noted that strategies need to be developed on a case-by-case basis, taking the features of the drive system into account to discern which rules would apply. Split drives, for example, have a biological control system on board, but some modeling would be needed to discern relevant parameters for comparing different drive systems. As to whether such a system would require a mitigation strategy, Dr. Akbari said that countermeasures are not necessary for split drives. Also, linked drives can be spatially confined if they are tied to private alleles. The question is whether the private allele exists in the target. He suggested starting with a feature that is inherently confinable and testing it in a split drive to see if it works; if it does not work, it would disappear. Insecticides could be an effective mitigation strategy. Dr. Messer agreed about this setting as the optimal way to test predictive models by going beyond the laboratory scale to a small island to ascertain migration patterns and so forth. Knowing that models work would be reassuring.

Dr. Piaggio spoke of the importance of recognizing that the field is progressing quickly. Communication between the government and practitioners keeps intellectual property flowing and drives progress. Experts can explain the state of the science, and the information can feed into a regulatory framework.

Are laboratory data available on the genetic stability of gene drives and whether they will persist in a wild population or whether the population will develop resistance? Dr. Messer thought that most genetic changes would weaken the drive. Dr. Gould spoke about "rescue drives" to preserve genetic fidelity, but that approach has never been tested. Dr. Akbari added that design criteria can help avoid the problem of resistance, such as targeting an essential gene and its effector. (The effector would not be copied during the homing process.) Drives can be designed to be more evolutionarily stable by building in an advantage to ensure spread of the drive. Modeling can help predict the persistence of the drive. With dengue, for example, it is possible to eliminate the virus if the cycle of infection is disrupted for even a few weeks.

Dr. Boris-Lawrie summed up the discussion, saying that conducting field trials with split drives might be a good first step. She clarified that the goal is not to carry out a contained trial in an ecosystem, but rather to jump from laboratory studies to field release. Dr. Piaggio said that although many insects can be housed in a small area, that approach would be challenging for rodent studies. She recommended introducing realistic ecological parameters for the target space to learn more and improve models through the ecological space.

Dr. B. Lee noted that much of the budget for the Human Genome Project was devoted to addressing ethical aspects of the study. Having funding set aside to address ethical concerns associated with the Human Genome Project drove progress. He asked about ways to include these ethical parameters to support more accurate model predictions for gene drive–modified organisms.

SESSION IV: ASSESSING RISK AND BENEFIT OF GENE DRIVE FIELD RELEASE

Panel Discussion

Moderator: Jason Delborne, Ph.D.

Panel Members: Sarah Hartley, Ph.D.; Keith Hayes, Ph.D.; Raul Medina, Ph.D.; and Bradley White, Ph.D.

This session focused on three questions:

- What strategies exist for risk and benefit assessments for gene drives or research with similar issues? What additional knowledge would be useful for conducting such assessments?
- What challenges exist for conducting environmental risk assessments for gene drive field release?
- What broader domains beyond environmental considerations should be considered when conducting a risk and benefit assessment for release of gene drives?

Guidelines for gene drive risk assessment as a key site of governance. Dr. Hartley, who is an interdisciplinary social scientist focused on the responsible governance of science, technology, and innovation, described risk assessment as being an important process. However, only an elite few are involved in creating risk-assessment guidelines. She emphasized the importance of including more voices in discussions of risk assessment, associated issues, and potential benefits.

Dr. Hartley said that the decision about whether to release the first gene drive organisms will likely be made by risk assessors operating in a regulatory framework. She argued that risk assessment guidelines are basically policies that have the appearance of being a scientific stage of risk governance while excluding a wide range of legitimate concerns and actors. Typically, public consultation does not occur until the very end of a long risk-assessment process. Dr. Hartley advised against relying solely on existing frameworks

that omit culturally specific considerations, including those of indigenous groups, since the concepts of risk and benefit depend upon the communities or people defining them.

Dr. Hartley and colleagues are writing a paper on the role of public engagement in risk assessment for gene drive organisms. More often than not, the main parties developing risk assessment guidelines are in Europe and the United States, despite the high likelihood that gene drive–modified organisms will be deployed in Africa. A great deal of thought is being given to the idea of opening up the process of guideline development for risk assessment to get input from communities where the frameworks will be adopted, often in Africa. Broadening the development of risk assessment guidelines is difficult but necessary. There are a few models for open processes.

It is also important to include socioeconomic risks in the assessment process. The Norwegian regulatory framework is the most advanced in terms of identifying and assessing socioeconomic risks.

Risk assessments often do not include discussions of potential benefits, although benefits matter a great deal to local people. Dr. Hartley said that consideration of benefits should go beyond economic assessment. Above all, risk assessments should be evidence-based and more than just an economic analysis that assigns monetary values to health and the environment.

Strategies for assessing risk and benefit for gene drive field release. Dr. Hayes spoke about quantitative ecological risk assessment. The primary challenge with ecological risk assessment in complex, novel situations is the paucity of data on wildlife, necessitating reliance on probabilistic risk assessment using the logic of the Bayesian approach.

There are alternative approaches for dealing with the challenges of novel, complex problems for which there is very little data. Dr. Hayes advocated using a probabilistic, quantitative approach for ecological risk assessment, which is essential for the scientific method, but there is value in structured qualitative approaches based on conceptual models, which can include fears and perceptions about consequences of possible events by conducting formal elicitation with various stakeholders. The outcomes of the qualitative approach can translate into the quantitative model to permit probabilistic risk adjustments. This approach takes time but makes the whole process amenable to comparing predictions against observations in the field and laboratory to update hypotheses. However, it is important to move toward quantitative techniques with early risk assessments.

Dr. Hayes discussed challenges associated with ecological risk assessment for gene drive field release. An advection-diffusion-reaction model will form the core of risk assessment for field release of a gene drive–modified organism, although this approach will be technically challenging and associated with significant uncertainty. In all likelihood, simulation is not sufficient for an adequate risk assessment; key parameters will require an empirical basis. In addition, monitoring will be necessary at large spatiotemporal scales, but rare events will be hard to detect and the process will be difficult and costly.

The assessment needs to consider where the transgenic organism could end up, how long it will last, and what it will interact with. A handful of models are addressing spatial scales, but significant uncertainty is associated with carrying capacity, advection, and competition. Simulation is not sufficient for an adequate risk assessment; there must be an empirical basis for key parameters. Rare events will be hard to detect and expensive to monitor.

Dr. Hayes identified some additional knowledge that would be useful, including data on population dynamics of one or more different species at varying temporal resolutions. In addition, Dr. Hayes pointed out that better use needs to be made of the data collected over the decades through hundreds of studies, but the information needs to be shared. Additional ecological data is needed on interacting species and the environment (e.g., if mosquitoes are removed from the ecosystem, what might the downstream effects be on geckos, lizards, spiders, bats, and insectivorous plants?). Knowledge on the ecological background is critical for input on risk assessment models.

Risk assessment for native vs. invasive species, limited gene drive spread, and gene flow. Dr. Medina focused on incorporating evolutionary ecological theory into pest control practices. Eradication of native and invasive species emulates drive spread and, therefore, may have implications for reproductive isolation as a strategy for confining gene drive releases.

Dr. Medina cited the example of cattle screwworm eradication in North and Central America. In North America, eradication of the screwworm fly with a gene drive might not significantly affect humans or other species, but in its endemic range in South America, the organism's absence might create new problems if other vectors flourish after a gene drive is introduced.

The partitioning of genetic variation matters, especially when assessing gene drive risks. This information is important not only to calculate the spread of a gene drive but also to understand that genetically distinct populations may differ in traits relevant to their control, such as resistance to a gene drive.

To improve the accuracy of risk assessment models, it is important to map gene divergence, not only geographically but also in terms of host-associated differentiation (HAD). Temporal or reproductive isolation can affect host specificity. For example, plants fruit at different times, leading to HAD in fruit flies. Insects and many other organisms, including some plants, have microbiotic components that are very important in their biology and may influence significant aspects of their physiology. Parameterizing HAD factors can improve risk models.

The Debug project for malaria eradication. Dr. White is a staff scientist at Verily Google Life Sciences, leading the development of a nontraditional product for mosquito control. The Debug project is releasing male mosquitoes infected with *Wolbachia* to try to suppress populations of *Aedes* mosquitoes through incompatible insect techniques. This

technology is being applied around the world to a variety of insects, including other mosquito species and agricultural pests.

For the Debug project, everyone is considered a stakeholder, including regulators at the national, state, local, and international levels. Dr. White said that for gene drive release, the regulatory hurdle is likely to be the easiest to overcome, because regulators evaluate on the basis of scientific evidence. It is more difficult to win over stakeholders who are involved in public health and mosquito control in localities where the release will occur. But the public is even more important. Assessments rarely include the risks and benefits for the public with these types of technologies. The public strongly supports the *Wolbachia* project because of the large potential benefit and low risk. Dr. White said he has been impressed by the gene drive community in general and how methodically it is trying to build evidence and think about the best way to bring this technology into the field.

Regarding regulatory risk assessment, Dr. White noted that there is scant attention given to the benefits of gene drives or the downside of the current situation. Many diseases carry a significant burden for affected populations. There is the nuisance factor, as well as economic risks and benefits that are rarely considered by regulators but are important to the public. He suggested positioning a technology by working out what the status quo is and why it is not working, instead of emphasizing low-probability, high-risk events.

Risks of gene drives include development of resistance and horizontal transfer; however, the risks are similar to those associated with insecticide use. Organisms will almost certainly develop resistance to the insecticide, and those genes can transfer to other species, conferring resistance. Insecticides also pose risks to human health, but none of those risks has stopped these products from getting approved. Dr. White recommended learning and communicating about the status quo and the potential benefits in terms of economics and nuisance reduction.

As for release of sterile or *Wolbachia*-infected male mosquitoes or use of gene drives, there is a potential for downstream effects on native species. Dr. White pointed out that these technologies are highly species-specific, which is a real advantage over almost all of the tools currently used for insect control.

When presenting a case to regulators, the public, or the public health workers or the mosquito-control technicians who would be implementing the technology, practitioners should frame the status quo, identify alternatives, and explain how those alternatives have been evaluated in the past. Dr. White also recommended gathering evidence about the technology, being conservative when predicting effectiveness, and being honest about the risks, benefits, and uncertainties.

General Discussion

Dr. Delborne asked about integrating community consultation with expert consultation in risk assessment. Qualitative models are amenable to a much broader range of input than mathematical equations are. Qualitative modeling would have an impact on engagement,

but the public is a diverse group. Some stakeholders (e.g., epidemiologists) have considerable knowledge of the problem to be solved, but others do not have in-depth knowledge. The public should be thought of in a much more nuanced way. Eliciting stakeholder values requires engaging and entering into a dialogue.

Matthew Porteus, M.D., Ph.D., asked Dr. Hayes to expand on the notion of establishing a buffer for risk and whether the buffer should be expressed as standard deviations or logarithms. Dr. Hayes responded that it is not a scientific question; it is a question about acceptance of the risk assessment. Dr. Hayes indicated that a more useful way to think of this is as a comparison of what is being proposed to what is being done now.

Dr. J. Collins asked about deciding who is an expert when it comes to risk assessment. Is everyone a stakeholder? Who are the decisionmakers? Dr. Hayes said that the range of stakeholders included would depend on the range of interests in the project and who would bear the brunt if something were to go wrong. It is important to have a variety of views, but only a limited set of stakeholders would be involved in assessing the risk of a more technical issue (e.g., genetic resistance). Also, different players should be involved at different stages. Dr. Hartley underscored the importance of having diverse representation by including local people as stakeholders. Regulators are not set up to take in community input. She recommended rethinking and pluralizing expertise before reaching out to stakeholders and publics.

Dr. Oye said that standards of justice would apply to decisions about whom to include in risk assessment activities such as gathering information to reduce uncertainty around the effects of gene drive release. The literature demonstrates that the quality of risk assessments improves through inclusion. The voices in the room should include those affected by the size of the footprint and shape of the field release. Dr. Medina advocated involving social scientists who are trained to capture diverse viewpoints and express those narratives as inputs for the technical component of risk assessment. Dr. Hartley said that the public articulates concerns in different ways using broader terms, but they are similar concerns. There are both ethical and substantive benefits of involving the public in risk assessment. Dr. Hayes said that a good risk assessment must be judged on both the outcomes (e.g., reflects a full range of hazards, includes estimates of uncertainty), and the process in terms of including a range of viewpoints.

Dr. Delborne asked Dr. White about surprises encountered as the Debug program moved from the laboratory to the field. Dr. White said he had not anticipated the degree of monitoring required and the high proportion of field trial costs involved in monitoring for adverse effects while collecting data to support robust statistical results to gauge efficacy.

Dr. Delborne asked a question of the panel that was based upon the discussions that have been taking place within the NExTRAC gene drive working group: he noted there isn't much discussion of how benefit assessments should take into account uncertainties and probabilities in the same way that risk assessments do. Dr. Hayes said there is no reason—from a methodologic standpoint—that benefit assessment would differ from risk assessment. However, in Australia for example, the focus is solely on the risks. That

approach may vary nation by nation. But methodologically, it should be possible to quantify benefits. Dr. Medina said that it is not difficult to calculate the risk of the status quo. The NExTRAC should think about and communicate the risk of gene drive release in comparison to the burden of disease. Dr. Hartley cautioned that quantifying benefits may be viewed by concerned groups as a potential bias to push a technology or chemicals. Additionally, what is valuable in fighting malaria might not be as beneficial in agriculture. Dr. Hayes continued this line of thought, saying that a range of technologies exists for solving a given problem. To minimize the perception of bias, discussions about benefits should cover a range of options, including the status quo. Dr. Cho pointed out an additional layer of complexity regarding potential benefits: in biomedical research, benefits often accrue to one group while risks accrue to others. Disadvantaged populations tend to bear the risks, while other populations reap the benefits.

ADJOURNMENT DAY 1

Dr. Whitley thanked the participants for their valuable contributions. The meeting adjourned at 4:45 p.m.

DAY 2

WELCOME

Richard Whitley, M.D.

Dr. Whitley called the meeting to order at 10:01 a.m. He re-stated the charge to the Gene Drives Working Group, and he indicated that the Gene Drives Working Group will continue to discuss issues related to the charge and will develop a draft report for consideration by the NExTRAC. Later in the afternoon, the NExTRAC will consider a draft report prepared by the Working Group to Establish a NExTRAC Framework.

SESSION V: U.S. AND INTERNATIONAL POLICY DISCUSSIONS AND OVERSIGHT FRAMEWORKS FOR RESEARCH INVOLVING GENE DRIVE FIELD RELEASE

Panel Discussion

Moderator: James Collins, Ph.D.

Panel Members: Elizabeth Heitman, Ph.D.; Stephanie James, Ph.D.; Lisa Knolhoff, Ph.D.; Todd Kuiken, Ph.D.; and Wadzanayi Mandivenyi, M.S.

Each panel member gave a brief presentation in response to the following questions:

- How has the state of conversation and knowledge (in terms of science and the regulatory framework) advanced since the time of the 2016 NASEM report?
- What knowledge, regulatory, and infrastructure gaps in the area of field release still exist, since the 2016 report? What advances have been made?
- What is the status of oversight for research involving field release of gene drives, domestically and internationally?

Overview of 2016 NASEM recommendations on gene drives. Dr. Heitman outlined the charge given to the authoring committee of the NASEM report. The main conclusion in the report was that, as of spring 2016, there was insufficient evidence to support the release of gene drive–modified organisms, but the potential for such technology justifies proceeding with laboratory research and highly controlled field trials. Notably, the report called on funders to coordinate and where possible collaborate to reduce gaps in knowledge across the spectrum of gene drive research and to consider other areas crucial for the responsible development and application of gene drive technology, including population genetics, evolutionary biology, ecosystem dynamics, modeling, ecological risk assessment, and public engagement.

The NASEM report emphasized that responsible science involves not only employing the best technical practices but also continuous examination, assessment, and integration of social, environmental, regulatory, and ethical issues. The report recommended a phased or stepwise approach to gene drive research, with risk assessment and public engagement occurring between phases and informing the research, governance, and next steps. The report also recommended the use of ecological risk assessment—a multifactorial evaluation of the potential benefits and harms that quantifies the probability of specific

outcomes, traces the patterns of cause and effect, identifies sources of uncertainty, and incorporates public concerns.

Dr. Heitman stressed that public engagement cannot be an afterthought. The NASEM report recommended that all those involved in the research enterprise have mechanisms and policies for how public engagement factors into research, risk assessment, and public policy decisions about gene drives. These mechanisms and policies should be part of the process from the outset.

The report identified the need for the U.S. government to clarify regulatory responsibility for overseeing research involving potential field release of gene drives, including agencies not currently included in the Coordinated Framework for the Regulation of Biotechnology. If researchers propose field release outside of the United States, then U.S. funders must consider those countries' regulatory systems (or lack thereof), the adequacy of those systems for controlling gene drive release, and the systems' incorporation of public engagement.

A one-size-fits-all approach to governance is not likely to be appropriate. The NASEM report recommended that the gene drive research enterprise examine whether and how international regulatory frameworks, national laws, nongovernment policies, and professional codes of conduct may be applied to gene drive research, particularly with regard to site selection, capacity building for responsible and inclusive governance systems, scientific and post-release surveillance, and stakeholder engagement. In terms of site selection, preference should be given to countries that have existing scientific capacity and a governance framework in place for safe investigation and development of gene drive organisms and gene drive-modified organisms, Dr. Heitman concluded.

Advances in gene drive policy and oversight. Dr. James explained that the Foundation for the NIH convened the Gene Drive Research Forum shortly after the 2016 NASEM report was published, to tackle cross-cutting issues and promote mutual learning. The Forum published guiding principles for gene drive research in 2017. It is currently crafting consensus definitions, exploring the use of registries, and considering mechanisms for stakeholder engagement. The Forum will soon publish a paper addressing principles for conducting gene drive field trials from the perspective of investigators.

The International Union for the Conservation of Nature and the Convention on Biological Diversity (CBD) are evaluating the potential effects of gene drives on the environment. The WHO recently recommended investigation of gene drives to address vector-driven disease and has an established evaluation process applicable to gene drive-modified vectors. Other international efforts include a comprehensive study of potential deployment of gene drive-modified mosquitoes for combating malaria in Africa; a WHO report, *Ethics and Vector-Borne Diseases*, that includes the topics of consent and public engagement around gene drives; and guidelines being developed by the European Food Safety Authority for risk assessment of gene drive-modified insects.

The African Union has undertaken regional harmonization, addressing some of the NASEM recommendations on strengthening regulatory authority and taking on the issue of cross-boundary movement. A multinational effort is underway to develop guidelines on biosafety and risk assessment for gene drives, with plans to first implement the guidelines in West Africa and then scale them up to the whole continent.

Given the potential public value of gene drives, underscored by the WHO and the African Union, Dr. James said there is a responsibility to address the remaining gaps through a coordinated, systematic, and targeted approach that takes into account the gene drive systems under consideration, the target organisms, and the environments. The Foundation launched the GeneConvene Global Collaboration this year to advance best practices and informed decision making to improve public health. The GeneConvene Virtual Institute offers resources for the field.

International oversight. Ms. Mandivenyi said CBD has engaged members in a broad discussion of synthetic biology, including the role of gene drives. In 2018, the Convention issued a decision that urged caution around engineered gene drives and reinforced the need to seek informed consent or approval in advance from local communities, especially indigenous communities, that could be affected by an environmental release. The Convention's decision would place conditions around such a release that encompass risk assessment, risk management, and consent.

The Risk Assessment Ad Hoc Technical Experts Group (AHTEG) determined that living modified organisms with engineered gene drives are within the scope of the Cartagena Protocol on Biosafety, which focuses on risk assessment and the potential negative effects of living modified organisms and drives CBD efforts. The AHTEG ascertained that the existing risk assessment methodology for genetically-modified mosquitoes may be applicable to other engineered gene drives, but specific challenges must be addressed, such as the following:

- How stable is the gene drive system, how will it be integrated into the target, and can the system sustain gene drives over time?
- What is the nature of the target organism, and how does it propagate?
- Is there sufficient information about the environment into which the gene drive-modified organism is being released?
- What risk assessment methods will be used?
- Have uncertainties been adequately addressed?
- How will data be collected and analyzed, and are there sufficient data for modeling? Is there guidance to support data collection and analysis?
- Are existing tools for risk management and monitoring applicable?

CBD has also taken stock of all the frameworks, guidance, and ongoing activities around the world on these topics. In terms of next steps, Ms. Mandivenyi said the discussion will be taken up by the Open-ended Working Group on the Post-2020 Global Biodiversity Framework, which will consider sustainable development goals and the contributions of biodiversity. The next CBD conference will include an in-depth review of synthetic biology. The Subsidiary Body on Scientific, Technical, and Technological Advice will

make recommendations based on the Risk Assessment AHTEG report. Future CBD conferences may request additional work related to gene drives.

Moving toward gene drive field trials. Dr. Kuiken outlined some key aspects of international deliberations. Notably, the WHO stressed the need for adequate funding to bolster existing regulatory systems in conjunction with funding the development of gene drive systems. Funding is also needed to support the WHO's recommendations for community engagement. The International Union for the Conservation of Nature's World Congress will put forth a motion at its tentatively scheduled meeting in January 2021, on principles and guidelines for synthetic biology and gene drive research. This motion includes the option of imposing moratoriums on gene drives and gene drive research.

Field trials in the United States for other geneticially-modified organisms could provide insights for gene drive research. A genetically-modified mosquito developed by Oxitec was approved for use by the Environmental Protection Agency (EPA), but only after regulatory oversight went from the USDA to the U.S. Food and Drug Administration (FDA) because of the uncertainty around regulatory authority for such a product. The Oxitec mosquito could be released in the field in the United States in 2021 in Texas and Florida. An interesting piece of the community engagement aspect of this release occurred in the Florida Keys. In the Florida Keys a referendum was voted on. A slight majority in the overall area was in favor of the release; however, the majority of voters in the area where the release is proposed to occur was not in favor of the release. Contained field trials underway of an organism intended to address disease in the American chestnut tree could offer insights on long-term monitoring. During Session III of this meeting, Dr. Piaggio discussed the possibility of a gene drive approach to controlling invasive rodents, but it remains unclear which regulatory body would have final jurisdiction over the application.

Dr. Kuiken called for experimental research stations to assess gene drives, and he expressed skepticism that islands would be ideal sites for field research. Wherever such research is conducted, investment in infrastructure is highly needed. Dr. Kuiken made the following observations:

- The U.S. government should consider re-engaging in international treaties and conventions. It is not a signatory to the CBD decision and is not represented on the Risk Assessment AHTEG.
- The U.S. regulatory system can handle review of gene drive applications, but some clarification is needed. Long-term monitoring requirements should be codified in regulations.
- A coordinated research strategy that funds ecological research at equivalent levels with gene drive development and draws on the knowledge of a broad range of experts is needed. Ecological risk research stations should be established to support the work needed.
- Field work should not be left for others to fund and conduct after gene drive development is complete.

U.S. government regulation of the diamondback moth. Dr. Knolhoff said that the Biotechnology Regulatory Services within USDA's Animal and Plant Health Inspection Service (APHIS) authorized a field trial in 2017 of the genetically engineered diamondback moth to combat the destruction of certain crops. The diamondback moth is a worldwide pest for which management costs are significant.

Researchers at Cornell University's Geneva, NY, campus conducted limited field trials of the genetically engineered moth, which wipes out the female moth population. They continue to assess the findings on the moth's dispersal, mating, biology, and competitiveness. As part of its evaluation of the research, Biotechnology Regulatory Services of APHIS produced an environmental assessment and impact statement for public comment. It considered the potential for persistence and spread.

In permitting the trial, Biotechnology Regulatory Services imposed a number of conditions. The principal investigator measured dispersal of the moths by using traps in the field, and Biotechnology Regulatory Services required regular reporting on the results. Because the moths tend to stay where host plants live, the permit specified that there must be a non–host-plant border around the test area, which Biotechnology Regulatory Services inspected. After the trial was completed, all the vegetative material involved was treated with insecticide and then tilled to ensure that the engineered moth could not persist.

General Discussion

In response to a question from Dr. Pilar Ossorio, there was discussion about remaining uncertainty around which federal agencies oversee which gene drive products, revealing a need to better understand how agencies communicate in order to determine which agency has the best mechanisms and expertise to evaluate a product in a given context. Dr. Kuiken noted that, in general, these proposed gene drives applications will be regulated, but it is important to determine which agency has the best expertise to evaluate the proposal. Jurisdiction for gene drive work can cross traditional boundaries. Dr. Heitman noted that he NASEM report recommended involving agencies that were not already part of the Coordinated Framework, such as the U.S. Fish and Wildlife Service and others within the Department of the Interior, such as the Parks Department.

Dr. Oye noted the importance of community engagement for gene drive applications, but noted the challenge of identifying the right communities and how that should be bound, as well as what kind of education is needed, from biosafety officers to principal investigators to the general public. Because stakeholders should be involved at many levels in the process of gathering information and making decisions, the communities engaged should correspond with the different types and levels of risk assessment, according to Dr. James. To elicit concerns and ensure that they are taken into account, an ecological risk assessment could draw from the community where the work is conducted, and Dr. James noted the important of co-development and co-ownership with relevant communities. She noted that funders should require that some of the budget for gene drive research should be focused on community engagement. Funders that signed the Gene Drive Research Forum's principles for gene drive research acknowledged that

obligation. Dr. Kuiken indicated that funders would also need to commit to long-term risk monitoring from the beginning of the project. Investigators cannot wait until the product is being tested in the field to secure funding for surveillance.

In response to a question from Dr. Mimi Riley, it was discussed that funders and developers must understand the importance of ecological risk assessment, but Dr. James notes that the approach to assessment depends on the product and the region where it would be applied. Once the product and region are specified, it is easier to assess the literature and identify the gaps and uncertainties to address. Dr. Kuiken noted that researchers should draw on the substantial experience with large-scale, long-term, dynamic ecosystem studies; the issue is ensuring the relevant experts are included and appropriate locations exist for conducting these studies, but he indicated he thinks the expertise and processes already exist. Existing information covers capacities required for managing a field release in specific locations and data on the receiving environment for gene drive–modified mosquitoes; and this information can be used to develop models.

Dr. J. Collins raised the questions of whether gene drive systems are qualitatively different from other types of research in terms of containment. One approach, according to Dr. Kuiken, is to begin with the premise that gene drives will spread in a field trial, then determine what can and should be done given that assumption. Regulatory pathways should address the requirements for field release. Because organisms have no respect for national boundaries, international benchmarks and minimal parameters that everyone can achieve should be established, as noted by Ms. Mandivenyi. She also noted that researchers and regulators should consider the balance between what they need to know to proceed and what would be nice to know.

Prompted by a question by Dr. Delborne, discussion turned to how community engagement during the risk assessment process can lay the groundwork for good community interactions. Input from local partners can contribute to co-development and co-ownership. In the United States, as noted by Dr. Knolhoff, the NEPA process require some kinds of engagement, such as formal public notice and comment periods, and the US Government also coordinates with local and state authorities. Dr. Delborne noted that there are no policy mechanisms for discussions of site selection, in advance, so he noted that more consideration is needed about methods for early community engagement.

Dr. Bloss noted that although the first day of the meeting elicited some enthusiasm for proposing remote islands for field trials, Dr. Kuiken expressed skepticism about whether that is the answer. Even islands are not completely isolated from contact. He said that more steps should be taken to gather more information on the environmental impact before studies are set up on islands. Dr. Kuiken noted that perhaps field trials should just be conceived of as releases, and perhaps the regulations and oversight should operate under that assumption. Dr. James added that site selection should also be influenced by the type of gene drive product.

Dr. Oye noted that gathering information will be complicated if all field trials are basically equivalent to a field release of the product; it will be difficult to evaluate risk

mitigation approaches if field trials are themselves releases. Dr. James proposed using a self-limiting version of the product as a first step. The process of risk assessment should be the same for all products, and the questions to be addressed would likely be similar for most. The degree of risk would be informed by the type of product and the potential test sites. She noted that there were ways to experimentally address many of these issues within containment and find ways to reduce the risk.

Dr. Heitman noted that the NASEM report sought to emphasize the importance of understanding the science of ecology in parallel with gene drive development and science. Integrating the two fields will require a significant reorganization of the current scientific enterprise. There is a clear need for more communication across disciplines.

SESSION VI: PUBLIC ENGAGEMENT—INPUT FROM LOCAL COMMUNITIES

Panel Discussion

Moderator: Cinnamon Bloss, Ph.D.

Panel Members: Steve Mulligan; Fredros Okumu, Ph.D.; and Beth Ranson

Each panel member gave a brief presentation in response to the following questions:

- What are the considerations of a local public health authority or communicator in the testing/use of modified organisms for the purpose of protecting public health?
- In your experiences, how have decisions been made at the local level regarding whether to test or use modified organisms?
- In your experiences, what were the primary concerns of relevant communities? What aspects of release of modified organisms had support of local communities?

Fresno, California, Consolidated Mosquito Abatement District. Mr. Mulligan described lessons learned from a large study involving several releases of male *Wolbachia*-infected mosquitoes. The first in 2016 involved the release in a bit more than one hundred acres in a residential area in Fresno. A second release occurred in 2019 and involved an area of over 2,100 acres. His agency recognized the need to control an invasive species of mosquito to prevent the potential spread of disease, and conventional methods had shown limited effectiveness.

Effective community engagement involves establishing public understanding. Information should be provided honestly, with clarity, and with transparency. Mr. Mulligan said the public should have a voice, but public opinion alone does not determine the final decision. The agency conducting the research should employ various methods of outreach and should encourage cooperation among jurisdictions. Community-wide outreach can include the news media, social media (although social media can sometimes generate misconceptions and backlash), websites, and on-site events. Community advocates can help spread information effectively. Surveys can reveal whether the information is reaching the target audience or needs to be revised. Mr. Mulligan emphasized that authorities must continuously combat misinformation.

To address concerns about safety, the agency can describe the regulatory process and criteria for the study, as well as the measures available for containment. The need for the study and who would potentially benefit should be explained.

Distrust in government can be a barrier. Local authorities tend to garner more public trust than those at higher levels. Communities distrust outsiders, especially those perceived as benefiting (profiting) from the research at the community's expense. Agencies should consider the impact of a proposed study on more disadvantaged communities. Support for research comes down to whether the community recognizes the potential benefits. In some cases, the proposed innovations might be viewed as preferable to existing methods (e.g., chemicals).

Mr. Mulligan summed up the lessons learned from his experience:

- Start community engagement early in the process.
- Discuss community concerns and potential benefits.
- Describe how the proposed intervention fits into the overall program.
- Be flexible and accommodate community concerns wherever possible.
- Anticipate the unexpected.
- Be transparent.

Florida Keys Mosquito Control District (FKMCD). Ms. Hanson noted that she left FKMCD earlier this year, so her remarks applied only to the community engagement process while she was with the organization. For more than 10 years, FKMCD has been seeking more effective methods for eradicating *Aedes aegypti* mosquitoes. Methods being employed in 2009 to combat a Dengue fever outbreak (methods against virus carrying mosquitoes) were not effective. Therefore, FKMCD turned to the use of genetically-modified mosquitoes in conjuction with Oxitec. Communication between FKMCD and the community has focused on explaining the benefits of using genetically-modified mosquitoes to reduce the mosquito population in conjunction with other methods currently in use (environmentally friendly chemicals, etc.) to prevent the spread of disease; unfortunately, education (reducing standing water, for example) does not always work.

FKMCD has jurisdiction over all the Florida Keys and has enjoyed a good relationship with local communities. It received approval from federal and state agencies to use the Oxitec mosquito for abatement but held additional public meetings and conducted outreach and engagement to demonstrate its respect for community concerns and to help people become comfortable with the proposed technology.

Ms. Hanson noted that at in-person town hall meetings, a vocal minority against the use of Oxitec mosquitoes drowned out, at times, the voices of many others. This resulted in attendees of these meetings with questions keaving without an opportunity to be better informed with respect to this technology. Webinars and phone-based meetings that allowed for all questions to be handled in a systematic approach helped to address this issue. This approach has been heightened during the COVID-19 pandemic.

Notably, the majority of Keys residents supported the use of *Wolbachia*-infected mosquitoes. Ms. Hanson suggested that fears of the Oxitec mosquito are based in part on a lack of understanding of genetic modification. Because of pushback against the use of Oxitec mosquitoes, FKMCD agreed to put forth a public referendum on the issue, although the results were nonbinding. Voting on a non-binding referendum demonstrated that the majority of the Keys community favored the technology, but a substantial number of people around Key West were against it, so FKMCD decided not to conduct testing in that area.

International perspective on community engagement. Dr. Okumu, an employee of the Ifakara Health Institute in Tanzania, said Tanzania has not released genetically-modified mosquitoes or gene drives and currently has no plans to do so, but the WHO and the African Union have expressed the importance of considering the potential of gene drive technology for controlling malaria. The Ifakara Health Institute seeks to improve community engagement in anticipation of future efforts and supports mechanisms to help people understand the technology.

Resistance to new technology is normal and expected. It is the responsibility of the "fast movers" in the field to provide information so people can make informed decisions, to set a precedent for ethical behavior, and to create systems that build significant capacity where there is little. These steps can be expensive but are also educational. Various challenges to engagement must be considered at the local level:

- *Language:* A common language is needed to help nonscientists understand the principles of gene drive research. Concepts such as gene drives do not translate easily into Swahili, for example. However, the concept of cross-breeding, for example, is familiar in an agricultural context, which could be a useful starting point.
- *Priorities:* Eradicating malaria is a top public health priority but might not be perceived as a major concern within a given community. Benefits should be described in the context of a community's desires and expectations.
- *Political buy-in:* Current events demonstrate that facts can be multidimensional and scientific opinions can be taken as political statements. It takes skill to engage people with different views who see the facts from different perspectives.
- *Variation:* A community is not monolithic; it is made up of people with diverse opinions. Some subsets of a community have more power than others, and some individuals drive local opinion.
- *Trust in science:* In Africa, trust in scientists remains high. Scientists recognize that in hypothesis-based research, the results of a study can change opinions. Training scientists in public engagement could be helpful.

General Discussion

Dr. Bloss asked the optimal timing of engagement and what some of the important considerations are. Ms. Ranson stated that based on her experiences with Oxitec, engagement started before the technology was a reasonable possibility, and that was too

early. With *Wolbachia*, they waited until regulatory approval was in place, and they found that to be more effective. Beginning in-depth discussions before the technology is a viable possibility means a lot of questions cannot be fully answered, which paves the way for misinformation to spread and take hold. Once a trial is approved, agencies can focus the discussion on the trial and why it was approved. Mr. Mulligan echoed this sentiment by indicating that there was an outbreak of an invasive mosquito species in Fresno that needed to be addressed by a new strategy. An experimental use permit had already been issued for *Wolbachia*-infected mosquitoes and therefore public engagement occurred after regulatory approval had been obtained. In response to a question from Dr. Adelman, Mr. Mulligan added that being flexible in community engagement means being responsive to community concerns, taking steps to address them when possible (e.g., reducing the number of male mosquitos in a particular area), or explaining why they cannot be addressed.

Dr. Cho asked Ms. Ranson why some in the Key West community had a different point of view about the proposed Oxitec approach, and why it was determined those differences should lead to an alternate outcome. Ms. Ranson indicated that particular community had been identified as an optimal location, which lead to an increase in misinformation going to those areas. As a result, and based on the outcome of the referendum, FKMCD decided not to implement the technology in that specific area out of respect for local wishes.

Dr. Delborne inquired as to whether there was any independent research that had been performed on the community outreach efforts that had been undertaken regarding the release of gene-modified mosquitoes. He also noted that any registry of gene drive efforts could include research on such community engagement efforts. Ms. Ranson indicated that there are published studies regarding the outreach efforts that were done in the Florida Keys.

Dr. J. Collins raised the issue of what extent consideration was given to the potential impact the release of the *Wolbachia*-infected mosquitoes might have on the environment (e.g., birds and other parts of the ecosystem), and whether the community was interested in thos issues. Mr. Mulligan indicated that the effect of mosquito control strategies on the health of native species (for example, bats or honeybees) was not an issue in residential communities in Fresno. In Florida, Ms. Ranson indicated that FKMCD works with numerous state and federal agencies on monitoring how a variety of treatments (not solely the release of modified organisms) affect the environment, particularly endangered and rare land and marine species, and FKMCD covers the cost of much of this monitoring.

Ms. Riley asked whether a consideration in the selection of communities is the history of that community with environmental justice issues. Mr. Mulligan said the initial focus in the selection of communities was where the problem was worse and where they had monitoring in place. Dr. Ossorio asked- when the community doesn't agree, what methods are used to decide what to do? Additionally, communities have different ways of making decisions (i.e., majority wins). Ms. Ranson said they decided the fairest way to

make a decision was a ballot referendum, rather than a survey administered by one of two groups that could potentially be biased. After a question from Dr. Oye, Dr. Okumu indicated that in the coming years additional knowledge will exist regarding this technology, ongoing work will continue to improve the regulatory systems, and that building capacity at the local level for decision making that take human issues into account will continue. Dr. Okumu hopes that the fast movers will not be so fixated on potential benefits that they downplay the risks and the unknowns, which are key for informed decision making. He noted that, in a democracy, the majority rules, but minorities may suffer. Public health data demonstrate that minorities are often more heavily affected by disease. It is the responsibility of those at the top to consider the rights of minorities.

SESSION VII: STRATEGIES FOR STAKEHOLDER AND PUBLIC ENGAGEMENT

Panel Discussion

Moderator: Cinnamon Bloss, Ph.D.

Panel Members: Abdoulaye Diabaté, Ph.D.; Thomas Dietz, Ph.D.; Jennifer Kuzma, Ph.D.; and James Lavery, Ph.D.

Each panel member gave a brief presentation in response to the following questions:

- What frameworks exist for public engagement for research that may involve similar issues/concerns as gene drives?
- What strategies have been used to consider appropriate locations for phased field release studies, carefully considering local community engagement? How effective have they been?
- What evidence can/should be presented to illustrate that engagement has been done appropriately?

Moving from persuasion to learning. Dr. Lavery said the main goal of most engagement frameworks around gene drive technology is to persuade the community to serve as a test site. The primary goal of engagement should be learning how an intervention might affect the community. Ultimately, governing bodies, not scientists, should use what they learn from engagement to make policies relevant to the community.

Much confusion persists about the relevant community to engage. One standard view of community for public health purposes recognizes existing social, cultural, geographical, and political associations that are independent of the proposed research interventions. Another standard view identifies a community by existing social ties, shared perspectives, or joint action, also independent of the research. These views raise the question of how an existing community can be defined as being uniquely relevant to interventions for opioid addiction, vaccine hesitancy, or gene drives, to name a few.

Dr. Lavery proposed defining "community" as a collection of individuals or organizations whose interests may be affected by the conduct or outcomes of research interventions. Therefore, the community is dynamic rather than predefined, changing

with the intervention. This approach also accounts for multiple layers and forms of legitimate authority. This approach provides an anchor for ethical analysis. In legal theory, individuals are harmed when their interests are blocked or set back. Ethically speaking, researchers should acknowledge and respond to stakeholders' interests; engagement is a step toward doing so. Furthermore, if engagement is perceived as a way to understand how stakeholders are affected by an intervention and to reveal and protect stakeholders' values, then the results of engagement can influence the design and parameters of the research and implementation. Stakeholder engagement is a partnership among many players, but only governments have the authority to make decisions on behalf of the community. Given that gene drive technology has the potential to cross borders, governments across jurisdictions must be involved in site selection.

Target Malaria's strategies for stakeholder and public health engagement. Dr. Diabaté said Target Malaria began efforts in 2012 toward introducing genetically-modified mosquitoes to combat malaria in several African countries. In 2019, it received approval to conduct a release using self-limiting technology as a first step toward implementing mosquitoes with self-sustaining gene drives.

Years of stakeholder engagement were key to Target Malaria's ability to go from its intial efforts to the release in 2019. The organization educated individuals at the village level in the areas selected for potential release, but it also worked at the national, regional, and international levels to lay the groundwork for understanding and future implementation. Over time, Target Malaria has succeeded in building trust and engaging many stakeholders around the common goal of eradicating malaria.

Dr. Diabaté outlined some hallmarks of good engagement:

- Inclusiveness
- Transparency
- Two-way dialogue (e.g., allowing people time to digest the information and come back with their questions later)
- Mutual respect
- Co-development (e.g., ensuring that people are informed so they can contribute their insights on how to solve local problems)
- Common goals

Linking analysis and public deliberation: Lessons from environmental assessment and decision making. Dr. Dietz said the purpose of engagement is to calibrate the science to the context. When considering whom to engage, it is necessary to look beyond scientific expertise to gather other kinds of insights and knowledge. Engagement also aims to ensure that processes are fair, so it is important to assess who has a voice, who decides what is favorable, what alternatives are considered, and how decisions are made.

In most situations where public concerns or skepticism arise, individuals usually do not disagree about the facts. Rather, there is lack of consensus on values and ethics. Dr. Dietz urged those proposing an intervention to think carefully about their basis for suggesting the intervention.

The 2016 NASEM report and other documents outline an iterative process for deliberation with the public. There is some consensus that, when done well, public participation improves the quality and legitimacy of decisions and builds the capacity of all involved to engage in the policy process. For engagement around gene drive research, the following concepts drawn from the literature might be particularly useful:

- Use deliberation to aid with "downscaling"—that is, applying what is known in general, in the abstract, in the laboratory, and in other contexts to a particular local context.
- An emphasis on diversity of participants, on environmental justice, and recognition that values matter as well as facts.
- Commit to ongoing evaluation of experiences with participation and deliberation to build the diagnostic questions and design principles.
- Use the literature to identify diagnostic questions to understand the nature of the problem and to apply design principles that extract generalizations to guide the process.

Dr. Dietz recommended the National Research Council's Public Participation in Environmental Assessment and Decision Making, which outlined 17 diagnostic questions and 15 design principles. Among the open questions for research are how to incorporate ethical analyses on an intervention's effects on animals other than humans (e.g., Michigan State University's animal studies program).

Deliberative processes are common at the local and regional levels but less so at the national and international levels. With the trend toward co-management and shared governance, there is an opportunity to frame the conversation about gene drive technology in the context of the problems it is intended to address. Funding is needed to support research around governance as well as technology; the findings can inform adaptive risk management. Dr. Dietz emphasized that diversity at the outset of engagement is important to subvert biases, and consideration must be given to values as well as facts.

Public engagement in biotechnology governance. Dr. Kuzma explained that formal decision making around gene drives and genetic modification is hampered by the lack of policy mechanisms and political will, perceptions that the public does not understand science and so needs to be persuaded to accept it, and fear of rejection of a proposed intervention. Her organization determined that stakeholders' beliefs about responsible research and innovation differ by group. Government and consumer groups tend to have more favorable impressions in terms of inclusiveness of the public in decision making and responsiveness to public concerns, among other factors, while industry and trade organizations have less favorable beliefs. Academia falls in the middle.

The concept of "academic capitalism"—the pressures of funding and competition—and fears that engagement will slow down innovation pose barriers to meaningful public engagement. Dr. Kuzma noted that the burden of proof often falls on those who conduct public engagement to demonstrate that engagement is effective, raising questions about

the intended goal of the engagement and for whom it should be effective. Flipping the question, Dr. Kuzma pointed out that perceptions of democracy, informed consent, social equity, and procedural justice all suffer when there is no public engagement. The risk assessment process also suffers, because public engagement requires thinking about who defines risk, how much information is enough, and what is considered safe—all questions that take values into account.

Dr. Kuzma argued that gene drive technology poses a dilemma, because the field needs data to proceed, despite the risks. There are serious deficiencies in the regulatory assessment approach that stem from a lack of humility and from systemic biases in interpretation and uncertainty. As a result, the substantial validity is challenged, making procedural validity more important. Greater public, stakeholder, external expert, and community engagement is necessary to correct for the bias of "techno-optimism" and to improve the risk assessment process for gene drive organisms.

Dr. Kuzma applied a risk assessment framework to the use of Oxitec mosquitos.[6] Her framework incorporated core policies of humility over hubris, responsible research and innovation, and criteria for good emerging risk governance. Other literature has determined the importance of using independent groups to facilitate engagement, to avoid conflicts of interest. Additional topics to consider include the need for legitimacy around the decision-making process, mechanisms to correct for bias and ensure balance in communication, and how to ensure social equity and a voice for the voiceless.

General Discussion

Dr. Bloss noted that several participants raised questions about how to evaluate the success (or failure) of public engagement (e.g., how do you know if it has been done well, are you ever done, etc.?). Dr. Lavery said most evaluation focuses only on procedure, but looking at stakeholders' interests provides a way to determine whether the process created value or revealed potential harms, for example. One way to assess public engagement is have you identified, articulated, and acknowledged those interests, and then have you characterized and executed those requisite obligations? Dr. Diabaté said no scientific instrument can measure the level of trust built in a community. He noted good engagement creates a dialogue, and, as a result, researchers are seen as reliable. Participants must be confident that mechanisms are in place to resolve any questions that arise.

Dr. Kuzma suggested applying the principles of program evaluation and conducting more studies on iterative engagement efforts to look at changes throughout the process. Dr. Dietz agreed that evaluation research is really critical. Dr. Lavery pointed out that big businesses spend a lot of money on data collection at the consumer level, which has transformed management. Financial support for gathering data on engagement would similarly provide an evidence base.

[6] Kuzma J. Procedurally robust risk assessment framework for novel genetically engineered organisms and gene drives. *Regulation & Governance*, 2019. doi:10.1111/rego.12245

Dr. Diabaté said his organization conducts audits to determine whether the community understands the topics of the engagement. Echoing Dr. Okumu, he said that translating the science of gene drive technology into local languages was a problem, so Target Malaria worked with language experts to create a lexicon that helps individuals better understand the science and the processes involved.

Prompted by a question from Dr. Oye, about the challenge of speaking to both local and global communities, Dr. Diabaté said that Target Malaria acknowledged how the research will affect people at every level and the need for outreach at every level. At the highest political level, decision makers must see the value of the work, or there will be push back against it. At the local level, the proposed intervention must be described in terms of the burden of disease and how individuals can shape the intervention. Also in response to a question from Dr. Oye about whether Target Malaria intend to use localized or global gene drives, Dr. Diabaté indicated that a localized drive is used early in the process, utilizing a phased approach to address community questions and concerns.

Dr. J. Collins asked Dr. Lavery about how broad the definition of communities who are affected should be. Dr. Lavery indicated that he prefers to think of stakeholders as individuals who have some interests in the conduct or outcomes of whatever is being implemented. Though that broadens the aperture of affected stakeholders, it now puts the solutions or options to adjudicate those decisions into the sphere of the political process, and there are mechanisms in place to resolve those questions.

Dr. D. Lee asked whether public opinion should always trump science, and noted that whether or not to approve a vaccine is not something most people would choose to put to a vote. Dr. Kuzma acknowledged that some groups deliberately spread misinformation to further their agenda. It should be acknowledged, however, that other groups are well informed, they understand the science behind the technology, and they raise legitimate concerns based upon a valid interpretation of the science or their own values; those who object to a proposed intervention should not automatically be dismissed.

Dr. Dietz echoed Dr. Kuzma's thoughts and pointed out that it is important to distinguish the results of public opinion polls from those of public deliberation. It falls to the research community to clearly lay out the ethical position behind the proposal rather than assume that the intervention is in the public interest. Dr. Lavery favored a model that distinguishes the person from the interests behind the position. The researcher can assess the underlying interest and determine whether there is an obligation to respond to it.

SESSION VIII: PRESENTATION OF THE DRAFT REPORT OF THE WORKING GROUP TO ESTABLISH A NExTRAC FRAMEWORK

Margaret Riley, J.D., and Gigi Gronvall, Ph.D., Framework Working Group Co-chairs

In December 2019, NIH Director Francis Collins, M.D., Ph.D., charged the NExTRAC Framework Working Group with describing effective approaches for prospectively identifying emerging biotechnologies or specific applications with reasonable potential to have important scientific, safety, or ethical considerations and conceptualizing a

framework for NExTRAC's deliberation of issues surrounding emerging biotechnologies and applications, including the following:

- Guiding principles for when an emerging biotechnology or its applications would significantly benefit from further public deliberation
- A potential process by which the NExTRAC will consider or evaluate any given emerging biotechnology or its applications

The efforts of the working group culminated in the Draft Report of the Working Group to Establish a NExTRAC Framework—the focus of this session.

Dr. Gronvall explained that the working group was not asked to scan the horizon but rather to propose effective processes for scanning the horizon for emerging biotechnologies or specific applications with reasonable potential to have important scientific, safety, or ethical considerations, with particular attention to the issues that would benefit from public deliberation by the NExTRAC. Useful steps for horizon scanning include identifying a signal using a variety of sources, applying criteria for filtering and prioritizing the results, assessing and disseminating the information, and identifying metrics for evaluating the overall process.

Ms. Riley said the working group examined the literature and determined that sources used for horizon scanning should be highly flexible, and should correlate with the technology assessed, be credible, and represent a diverse set of voices. Quantitative and qualitative approaches to filtering are important, as are mechanisms for validating the horizon scanning techniques.

Dr. Gronvall noted that identifying emerging technologies for NExTRAC consideration should highlight areas of convergence in which distinct technologies begin to align and might require a response from NIH. She said that the NExTRAC would be a good sounding board for assessing such topics.

Ms. Riley observed that the most effective horizon scanning process would build on previous work and be iterative in nature. Scanning should include explicit methods for mitigating the effects of biases and psychological heuristics. Rather than focusing on hypothetical technologies, the scanning process should look at technologies that are likely to emerge in five to ten years. The proposed approach builds in periodic reviews to allow for evaluation and revision of the processes.

Dr. Gronvall said the working group was asked to develop guiding principles for when an emerging biotechnology or its applications would significantly benefit from further public deliberation, but such principles would likely overlap with existing principles. Instead, the working group created prompts intended to bridge the gap to existing scientific, safety, and bioethical principles. Prompts include, for example, recognition that a biotechnology is likely to have widespread use or that there is a lack of awareness or consent. The prompts do not function as a checklist and are not ranked in importance, nor do they represent strict criteria for identifying emerging biotechnologies.

Ms. Riley said the working group aimed to preserve the concept of guiding principles by developing a table describing the values that underlie the prompts. These include familiar ethical principles, such as nonmaleficence, equity, and fairness; concepts related to the technology, such as relevance and timeliness; and aspects of public deliberation, such as oversight and transparency.

Dr. Gronvall described a proposed process for NExTRAC deliberation, noting that the prompts could arise from various sources. A horizon scan could inform the charge to the NExTRAC, which would then evaluate the scientific, safety, and ethical considerations, determine what kind of public deliberation is needed, and determine how public engagement would be of benefit and identify effective methods. The framework would be flexible enough to adjust to a range of possible future charges. It would allow for gathering public input and would result in recommendations and a report. Ms. Riley thanked the NIH staff for supporting the working group.

PUBLIC COMMENTS

Beth Tuck, Executive Director of the nonprofit, community-based science education and innovation center Genspace, observed that the workshop included many calls for community engagement. Robust methods are needed for such engagement. The public needs access to experts who can unpack scientific advances and distinguish them from media hype. Located in Brooklyn, NY, Genspace is open to anyone seeking to learn the fundamentals of science and the skills to engage with scientists. Its goal is to democratize biotechnology to include people from various backgrounds. Ms. Tuck said that community science organizations like Genspace are well positioned to take part in public deliberations.

Notably, people in the community biology movement have been working for several years to develop a handbook on biosafety. Ms. Tuck said the handbook is a model for development of community-driven, practice-based, biosafety guidance for community laboratories.

Ms. Tuck proposed that NIH, the NExTRAC, and others partner with Genspace around public engagement, because Genspace has access to a diverse, highly engaged community of people who care deeply about synthetic biology, neurotechnology, artificial intelligence, and other emerging fields of science. The community includes designers, economists, teachers, cybersecurity professionals, home-schooling families, and many others who want to learn about and contribute their expertise to the conversation. Community members come from diverse backgrounds and could identify emerging technologies of interest.

Gerald Epstein, Ph.D., said that the NExTRAC was charged with assessing the biosafety, social, and ethical issues associated with emerging biotechnologies. Security is notably absent, presumably because another federal advisory committee, the National Science Advisory Board for Biosecurity (NSABB), addresses it. Dr. Epstein said the separation of security from NExTRAC's mission is artificial, particularly because the NExTRAC will look at biotechnologies early in their development, possibly before any potential harm is known. Security threats stem from the deliberate use of technology for harm, which in

turn threatens safety and poses social and ethical problems. Therefore, he argued that security falls within the NExTRAC's purview and should be explicitly acknowledged.

If NIH intends to assign security issues exclusively to the NSABB, Dr. Epstein continued, that should be explicitly stated, and that body should have a procedure equivalent to NExTRAC's framework for identifying biotechnologies of concern, making policy decisions, and establishing governance.

Dr. Epstein said workshop participants used the term "public" frequently. Within the perspective of the U.S. government, "public" refers to everything that is not the U.S. federal government. In other situations, the word is intended to mean those who might not have a voice or who would otherwise be excluded from the conversation. It may be intended as a counterpoint to the opinions of experts from government agencies, those within the scientific community, or those who have a vested interest in a technology. Dr. Epstein recommended that NExTRAC's framework clearly describe the meaning of the term "public." The terms "public" and "community" are complicated and should be carefully considered.

Dr. Whitley noted that written public comments have also been received and provided to NExTRAC members and will be posted to the OSP website.

NExTRAC DELIBERATION OF THE DRAFT REPORT OF THE WORKING GROUP TO ESTABLISH A NExTRAC FRAMEWORK

In response to the oral public comments, Dr. Cho said that the draft document should at least reference security and recommend that biosecurity experts be included in NExTRAC deliberations. In addition, Dr. Cho said the draft cannot address the interpretation of the term "public" in all instances but could clarify that public engagement should include scientists and developers.

Dr. Oye noted that the issue of security was discussed at the first NExTRAC meeting. Dr. Gronvall noted that some NExTRAC members have security expertise. She believes that security is one of several considerations for the NExTRAC, whereas it is the primary concern of the NSABB. Dr. Tucker said NIH can further discuss where security fits in to early assessment of emerging biotechnologies, but the issues in the working group's report reflect the language contained in the charter of the committee. Dr. Oye agreed with the suggestion to explicitly broaden NExTRAC's scope to include potential security threats. Dr. Ossoio said a heightened degree of concern about biosecurity or national security suggests it could be added to the report.

Dr. Lewis-Hall added that many other agencies have relevant insights and perspectives that could be valuable for NExTRAC deliberations. She proposed that the horizon scan include outreach to relevant agencies, which may be a way to align work across disparate groups. Ms. Riley agreed, and Dr. Gronvall said that input on the horizon scan can come from outside NIH.

Dr. Adelman said workshop participants have made the case that public deliberation or discourse is distinct from public engagement, in which interests and values are identified. It is not clear that NIH has conducted any public engagement on gene drive technology so far, and Dr. Adelman asked how NIH should do so. Ms. Riley replied that each charge would influence the type of public deliberation needed, and Dr. Gronvall agreed.

Leigh Turner, Ph.D., said that getting feedback through public comments, holding town halls, and ensuring broader representation by including civic society groups are three ways to begin to address the issue of meaningful public engagement. Community engagement is challenging for academics and others, but it is constructive and encourages in-depth thinking about important topics. He also noted that the public comments heard immediately prior to this session opened up new issues that the committee might not have otherwise discussed, so the importance of this engagement is obvious.

Kim Thiboldeaux pointed out that the current discussion is happening at a time of racial reckoning in this country, and organizations like hers are talking more and more about health equity and social determinants of health. There is a crisis of faith in government and scientists. Ms. Thiboldeaux said that more intentional and aggressive steps can be taken to engage diverse communities, ensure transparency, build trust, restore faith, and improve dialogue. It is important to invest in people, providing them with knowledge and training to advocate for scientific advances.

Ms. Thiboldeaux said that in the United States, discussions of science are deliberately separated from those of reimbursement for medical expenses, but in other countries, those discussions are not separate. The U.S. approach leads to the release of remarkable medical advances that only the wealthy can afford. It is incumbent on scientific and government agencies to take into account access, affordability, and reimbursement so that they are not contributing to the widening gaps in health care.

Dr. Cho noted that NExTRAC's position within NIH, the main funder of biotechnology research, is in some ways a built-in conflict of interest. Although limited in its ability to propose and undertake some forms of public deliberations, the NExTRAC can pursue other activities that supplement such deliberation.

Kafui Dzirasa, M.D., Ph.D., stated that NIH can offer important lessons and models. For example, the NIH *All of Us* Research Program built in mechanisms for engaging broad, diverse communities in research. NIH can use existing platforms to get feedback on emerging biotechnology.

Lorraine Albritton, Ph.D., said that the working group discussed how the NExTRAC could provide input into horizon scanning. She mentioned that the draft document should spell out the mechanism for doing so, because otherwise it is not clear how the NExTRAC would decide whether a new topic should be flagged for NIH consideration. Dr. Adelman followed up on this point, asking for the addition of specific language to articulate this point, and Dr. B. Lee asked about operationalization and implementation of Figure 2, in particular. Dr. Tucker pointed out specific wording in the draft added in

response to the working group's deliberations that clarifies the role of the NExTRAC as an important input into horizon scanning conducted by NIH, and the Committee's charter also responds to some of the concerns. How the framework is implemented depends on the charge. Ms. Riley noted that the mechanics of the process should be distinguished from the framework; if the mechanics are too specific, they could limit the application of the framework.

Dr. Adelman proposed a change to the language in the report to add the concept that NExTRAC members are encouraged to bring their ideas for issues the Committee should address to NIH as they consider potential charges. Several members agreed with the suggestion, saying it would put into writing the intention depicted by Figure 2 to ensure that the dialogue goes both ways.

Dr. Lewis-Hall asked whether any of the prompts for consideration address the potential for the technology to meet a significant unmet need in terms of health outcomes or whether the prompts only focus on technologies that could further inequities. Dr. Tucker pointed to language in the draft that speaks to promoting health equity and avoiding exacerbation of social determinants of health. The prompt describing uneven distribution of impacts specifies that the potential benefits of emerging biotechnology should be considered. Ms. Riley said the language could be made to be more explicit with slight editing.

Dr. D. Lee asked whether the proposed framework should describe explicitly how the NExTRAC can interact with others in the Coordinated Framework. Ms. Riley said such interaction would depend on both the charge and on the topic under consideration. In its evaluation of gene drive technology, for example, the NExTRAC could recommend more interaction with the Coordinated Framework.

Dr. Oye moved that NExTRAC members vote to approve the draft document with edits suggested by the committee during this discussion that have been captured by NIH staff. Specifically, Dr. Gronvall and Ms. Riley clarified that these included:

- Addition of edits suggested by Dr. Adelman related to NExTRAC members being encouraged to bring their ideas from their own horizon scanning to NIH for consideration of potential future charges, and
- Tweaks to language related to health equity and engagement of diverse communities raised by Dr. Lewis-Hall.

Dr. Albritton seconded the motion. Dr. Whitley called the roll.

> **Vote:** NExTRAC members voted to approve the draft document with the edits described.

ADJOURNMENT
Carrie Wolinetz, Ph.D., and Richard Whitley, M.D.

Dr. Whitley thanked the participants for the highly educational meeting. Dr. Wolinetz thanked the NExTRAC members for their continued dedication and NIH staff for making sure the meeting went smoothly. The meeting was adjourned at 5:12 p.m.

Jessica M. Tucker -S

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Date: 2021.02.05 07:12:07 -05'00'

Date: _____

Jessica Tucker, Ph.D.
NExTRAC Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and the following Attachments are accurate and complete.

This Minutes document will be considered formally by NExTRAC; any corrections or notations will be incorporated into the Minutes.

Date: 2/5/2021

Richard Whitley, M.D.
Chair, Novel and Exceptional Technology and Research Advisory Committee

ACRONYMS AND ABBREVIATIONS

ABSA	Association for Biosafety and Biosecurity
ACG	Arthropod Containment Guidelines
ACL	arthropod containment level
AHTEG	Ad Hoc Technical Experts Group
BSL	Biosafety Level
BSO	biosafety officer
CBD	Convention on Biologic Diversity
COI	conflict of interest
CRISPR	clustered regularly interspaced short palindromic repeats
DIY	do-it-yourself
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
EU	European Union
FAA	Federal Aviation Administration
FDA	U.S. Food and Drug Administration
FKMCD	Florida Keys Mosquito Control District
HAD	host-associated differentiation
IBC	Institutional Biosafety Committee
iGEM	International Genetically Engineered Machine
MEG	magnetoencephalography
NASEM	National Academies of Sciences, Engineering, and Medicine
NIH	National Institutes of Health
NExTRAC	Novel and Exceptional Technology and Research Advisory Committee
OSP	Office of Science Policy
RAC	Recombinant DNA Advisory Committee
SOP	standard operating procedure
RNA	ribonucleic acid
Syn bio	synthetic biology
USDA	U.S. Department of Agriculture
WHO	World Health Organization

ATTACHMENT I: NOVEL AND EXCEPTIONAL TECHNOLOGY AND RESEARCH ADVISORY COMMITTEE ROSTER

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