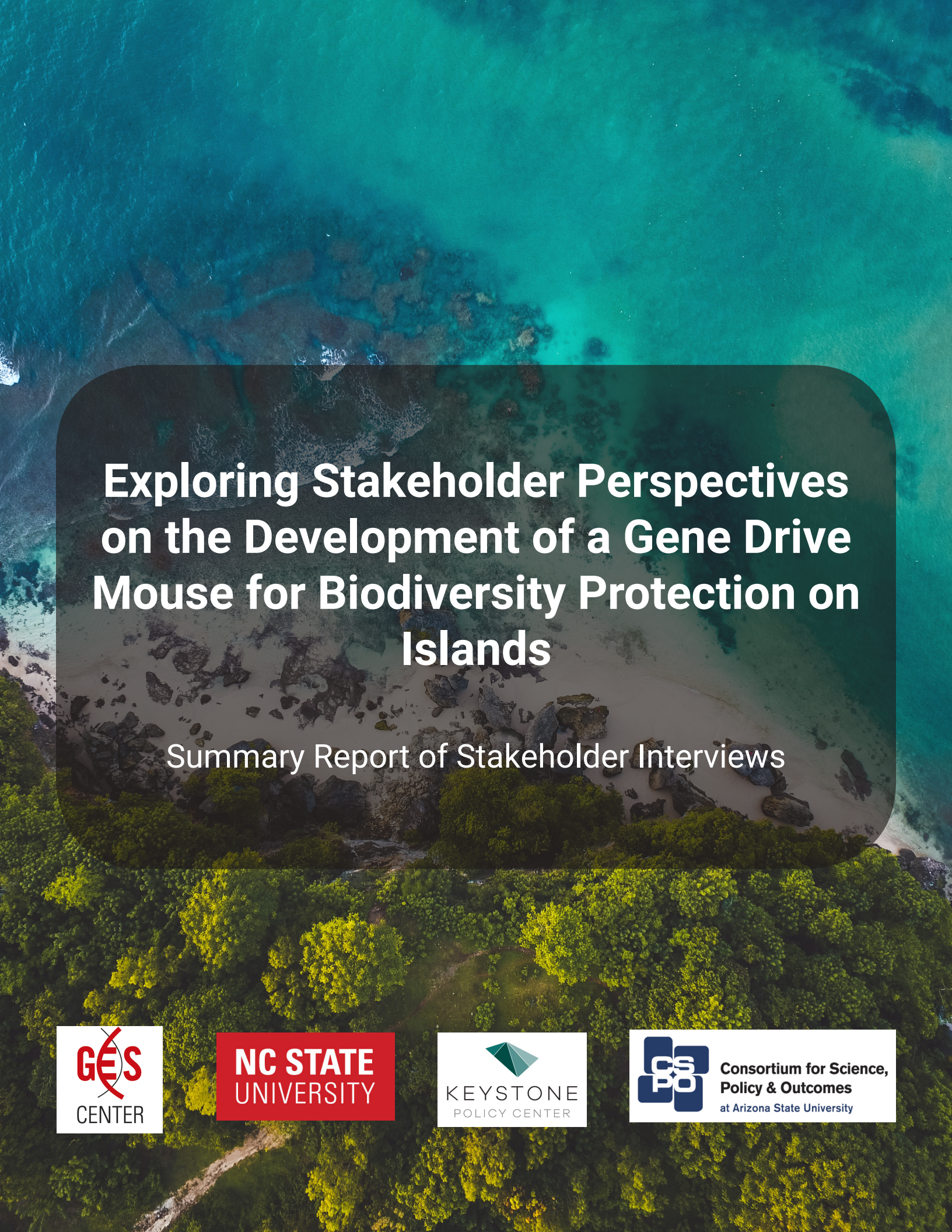

Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection on Islands

Summary Report of Stakeholder Interviews

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at Arizona State University

Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection on Islands: Summary Report of Stakeholder Interviews

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Available for download at the Genetic Engineering and Society Center website
http://go.ncsu.edu/ges-gene-drive-landscape

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Executive Summary

Introduction

This report summarizes the results of a landscape analysis of stakeholder interests, beliefs, and values surrounding the development of a gene drive mouse. Mice offer an ideal genetic model for exploring the possibility of developing a synthetic gene drive in mammals, and as pests, they pose challenges to human health (through disease transmission), agricultural yields and storage, and biodiversity, especially on islands where they are not native. In line with the guidance of the National Academies of Sciences, Engineering, and Medicine report on gene drive research[4], if research on gene drives in mice were to progress to a field trial, an island ecosystem would offer an additional level of physical containment. Thus, the focal application for this landscape analysis is the potential for a gene drive mouse to suppress an invasive mouse population on an island that poses a biodiversity threat.

This exploration of stakeholder perspectives is intended to inform laboratory research underway to develop a gene drive mouse through genetic engineering, creating an inheritance mechanism that biases future generations to be male (or female) only, thereby achieving invasive rodent population suppression by attrition. In addition, this landscape analysis is intended to inform the design of a stakeholder engagement meeting to be hosted at North Carolina State University in 2019. Both the stakeholder analysis and laboratory research are funded through the United States Defense Advanced Research Projects Agency's (DARPA) Safe Genes program (SAFE-FP-005). Safe Genes performer teams work across three primary technical focus areas to develop tools and methodologies to control, counter, and even reverse the effects of genome editing—including gene drives—in biological systems across scales. The performer team led by NC State University was awarded support for a project entitled, "Restoring Ecosystems and Biodiversity through Development of Safe and Effective Gene Drive Technologies." Delborne, a faculty member at NC State, is a Co-Principal Investigator of this award, and the Keystone Policy Center and Dr. Mahmud Farooque have received financial support as consultants.

This is a report to the Safe Genes project funders and researchers and the NC State-led performer team exploring the potential to develop a gene drive mouse for protecting island biodiversity. For transparency, the report is publicly available on the website of North Carolina State University's Genetic Engineering and Society Center (http://go.ncsu.edu/ges-gene-drive-landscape).

Methodology

The landscape analysis of stakeholder perspectives was conducted by a team comprised of professionals, interns, faculty, and students from North Carolina State University, Arizona State University, and Keystone Policy Center. Using online research and existing stakeholder networks, the team identified and then interviewed 20 stakeholders from academic, government, and NGO sectors within and across broad categories of overlapping interest and experience in gene editing, gene drives, and biodiversity protection. Interviews were conducted by phone or an audio web interface, recorded for accuracy, fully or partially transcribed, coded, and analyzed for key insights. Goals were to inform 1) technical decisions about developing gene drive mice for protecting island biodiversity and 2) the design of future community engagement activities that would occur prior to a field trial on an island. Interview respondents answered questions regarding: a) attitudes toward biodiversity protec-

[4] National Academies of Sciences, Engineering, and Medicine (NASEM), 2016, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. Washington, D.C.: National Academies Press.

tion, gene editing and gene drives; b) benefits and risks of gene drives for invasive rodent control; c) scenarios for the use of gene drives for invasive rodent control; d) sources of trustworthy information; e) engagement experience and perspectives; and e) understandings of governance frameworks that might apply to gene drive rodents.

Conclusions and Recommendations

The landscape analysis, which reflects the perspectives of the 20 interviewed stakeholders, suggests the following conclusions and recommendations for those funding or developing a gene drive mouse for biodiversity protection.

1. RISKS & BENEFITS

1.1 Key perceived risks included the actual efficacy of gene drives (too low or too high), off-target impacts, the ability to control gene drives, the unknowns, and broader implications for health, the environment, and society.

1.2 Key perceived benefits, in addition to the benefits of invasive rodent eradication for island biodiversity protection, focused on how gene drives might have advantages over existing eradication methods in terms of efficiency, efficacy, scalability, cost-effectiveness, and reduction of off-target effects.

1.3 Risk assessment should evaluate benefits and risks of gene drive mice **in comparison to other methodologies for eradication** and enable those engaging with communities and stakeholders to answer questions about risks, benefits, and uncertainties.

2. SCENARIOS FOR ISLAND SELECTION & GENE DRIVE DEVELOPMENT

2.1 For those supportive of field trials, a phased approach of beginning trials in simple island environments, followed by more complex island environments, was generally recommended. Stakeholders described benefits of enacting field trials in simple island environments (where control is easier, traditional eradication could be deployed, and success is more likely) but also described the ultimate benefit of demonstrating the technology in complex island environments (where the advantages of a gene drive strategy would be clear in comparison to existing technologies).

2.2 For those opposed to gene drives, there was no recommended safe nor appropriate scenario in which to begin field trials.

2.3 Stakeholders differed in their beliefs about impacts on public perceptions of whether a gene drive is transgenic or cisgenic. Many noted that **gene drives will be linked to broad public debates about GMOs regardless of the specifics of the technology.**

3. TRUST

3.1 No source of information was seen as categorically unbiased, with calls for transparency across sectors as a common precursor for trust. Themes of bias, conflict of interest, and transparency strongly influenced discussions of trust.

3.2 Because no for-profit entities are yet visible in gene drive research, critique focused on other markers of bias, such as funding sources (e.g., the military), the "interests" of scientific teams in promoting their research and technology, and prior value commitments of NGOs and other political actors.

3.3 Stakeholders tended to trust formal, expert sources for information, such as university researchers and government agencies, while perceiving citizens as primarily trusting friends, family, and local community networks. Relatedly, they believed that citizens have different metrics for risks and benefits than experts. If accurate, these differences suggest that **engagement activities focused solely on communication by formal experts may not be sufficient**

for broader public engagement.

4. ENGAGEMENT

4.1 Many stakeholders emphasized the **importance of involving local entities as trusted sources of information.** One strategy would be to engage local communities well before plans for field trials are finalized. Another strategy would be to recognize the need for a significant pause in field trial planning once a field trial site is identified, with time and resources allocated to allow engagement among scientists, community leaders, and biodiversity advocates. Engagement of relevant stakeholders and communities remains important even in cases where field trials are planned for uninhabited islands.

4.2 Stakeholders said **it was important not to be too "pushy" about the issue and agenda that are the focus of engagement, especially if those facilitating engagement come from outside the community**. Alignment between project goals and community values and priorities is critical.

4.3 It is important for community participants to feel that sharing their perspectives and opinions is influential as a "tool for actually determining an outcome"[5] and that they are **not serving a role of simply "checking off a box for community engagement."** If engagement ultimately is inhibitory (i.e., the location is not chosen due to a community's lack of acceptance), this would be consistent with the purpose of engagement in enabling the community to help determine both whether and how a trial is conducted.

5. GOVERNANCE

5.1 Stakeholders communicated many different views about how governance should proceed, often emphasizing the priority of one scale of governance over another. **Any emphasis on one scale of governance over others is likely to foster criticism, which points to the importance of a strategy that attends to multiple scales of governance at each step**. For example, those in favor of a gene drive moratorium often prioritized the achievement of international governance (a very challenging task), while those with more supportive views of the technology seemed to emphasize the importance of local governance or existing national regulatory structures.

5.2 Stakeholders noted that **it may be necessary to incorporate national level agencies not previously involved in the governance of biotechnology**. One stakeholder commented, "For example, for control of a modified invasive species on an island, it is not clear to me which agency would be responsible. The Fish and Wildlife Service is not even a member of the Coordinated Framework, where it might make most sense to make these decisions."

5.3 Some stakeholders objected to the framing of the interviews as narrowly focused on gene drive rodents for biodiversity protection, mentioning **greater concerns regarding their potential applications for agricultural and military purpose**s. They emphasized seeing gene drives as a "platform technology" with huge implications. This presents a challenge to a process that emphasizes careful consideration of risks and benefits of a particular application of the technology (such as gene drive rodents for biodiversity protection).

5.4 Stakeholders differed in their view of the potential for adaptive management in the face of uncertainty. Some expressed a desire for reducing scientific, regulatory, social, and ecological uncertainty prior to field trials (and further laboratory research, in some cases). Others preferred a phased and cautious approach that would reveal potential problems in ways that could be managed as research moved toward broader deployment. At the extreme, one stakeholder said, "it doesn't matter because...there is no safe way to experiment with these technologies in the wild." This reflects different value orientations as well as different levels of trust in decisions made about managing risks during research and field

[5] Unless otherwise noted, text in quotation marks represents direct quotations from stakeholder interviews.

trials.

While these conclusions and recommendations are drawn specifically from stakeholder interviews regarding a gene drive mouse for biodiversity protection on islands, many are likely to apply to other gene drive research projects with potential applications in human health, food and agriculture, and defense. However, because interviews did not specifically explore perspectives on other applications, caution should be exercised in assuming transferability of these points. For some stakeholders, significant concerns about gene drives as a platform technology will likely endure regardless of applications. For others, the perceived risks, benefits and tradeoffs of a gene drive mouse for island biodiversity protection may differ from those perceived for other gene drive applications—for example, a gene drive mosquito for reduction of malaria incidence in humans in mainland settings.

Accordingly, a final recommendation of the engagement team that authored this report is for continued support of stakeholder and community engagement as an essential component of gene drive research in order to 1) create an understanding of the various perspectives associated with gene drives, in general, as well as with context-specific applications, and 2) ensure that these perspectives inform decisions regarding whether and how gene drives are developed, tested, and used.

Chapter 1: Introduction

Chapter 1: Introduction

1a. Gene Drives and Engagement

A gene drive is a biased-inheritance mechanism through which certain genetic traits have an increased likelihood of being inherited. Whereas normal traits have an approximately 50% chance of being inherited by offspring, certain gene drives have the potential to result in 100% inheritance. Gene drives can occur naturally in populations, but scientists are working to develop new drives in the lab through genetic engineering. Potential applications of these genetically engineered drives include eradicating mosquitoes to address the spread of human and avian malaria and eliminating invasive rodents on islands.

Gene drives have implications for a wide range of fields, including public health, ecology, national security, and more. As a result, communities, stakeholders, and the broader public will likely be following their development, whether with enthusiasm, opposition, concerned scrutiny, or a combination of all of the above. The National Academies of Sciences, Engineering, and Medicine (NASEM) has recommended incorporating strategic, systematic and sustained engagement of communities, stakeholders, and broader publics early in the innovation process for gene drives[6].

The phased testing approach detailed in NASEM's (2016) *Gene Drives on the Horizon* report, which was inspired by the World Health Organization's (2014) *Guidance for Testing Genetically Modified Mosquitoes*, recommends that technical research proceed in phases, with careful attention to ecological risk assessment and public engagement at every step. While much of science tends to focus on activities to ensure the safety and predictable function of gene drive technology, technical excellence is insufficient on its own, as it could be derailed or curtailed by inadequate attention to engaging the communities, stakeholders, and publics that help to define the governance landscape and inform scientists' technical pursuits. Figure 1 presents the definitions of communities, stakeholders and publics described in the NASEM (2016) report.

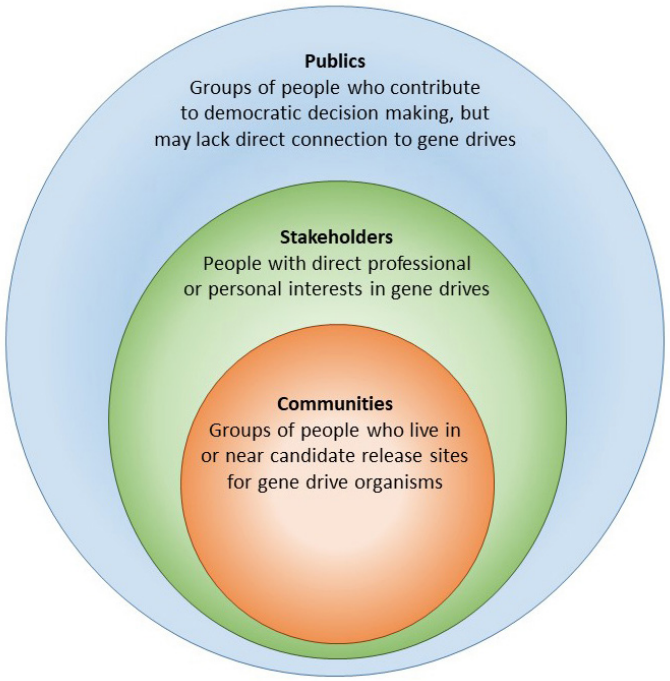


Figure 1. **Defining publics, stakeholders and communities** (graphic adapted from NASEM, 2016)

This summary report of stakeholder interviews occupies an early phase of feedback from stakeholder engagement to researchers and funders making decisions about innovation pathways, risk assessments, and product design. Stakeholders are the focus for two reasons: 1) their perspectives are highly informed by expert knowledge that differs from the knowledge of the Safe Genes project team, and 2) because gene drive development in mice is still in its infancy, there are not yet communities to engage.

[6] National Academies of Sciences, Engineering, and Medicine (NASEM), 2016, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. Washington, D.C.: National Academies Press.

1b. The DARPA Safe Genes Program

As described on its website, the U.S. Defense Advanced Research Projects Agency (DARPA) Safe Genes program (https://www.darpa.mil/program/safe-genes) "supports force protection and military health and readiness by protecting Service members from accidental or intentional misuse of genome editing technologies. Additional work will leverage advances in gene editing technology to expedite development of advanced prophylactic and therapeutic treatments against gene editors. Advances within the program will ensure the United States remains at the vanguard of the broadly accessible and rapidly progressing field of genome editing. Safe Genes performer teams work across three primary technical focus areas to develop tools and methodologies to control, counter, and even reverse the effects of genome editing—including gene drives—in biological systems across scales."

A North Carolina State University (NCSU)-led Safe Genes team aims to develop and test a mammalian gene drive system in mice. If successful, the work will provide insight into the fundamentals of gene drive technologies and expand the tools available to manage invasive species, like rodents, that threaten biodiversity and human food security, and that serve as potential reservoirs of infectious diseases affecting native animal and human populations. The project is exploring both the feasibility and suitability of the use of gene drives to create a self-limiting gene-drive modified mouse that biases future generations to produce offspring of only a single sex (male or female depending on the mechanism), thereby achieving invasive rodent population eradication by attrition. Note, however, that the Safe Genes program does not fund any environmental release of a gene drive-modified organism.

In addition to its technical team, which includes partners from the Commonwealth Scientific and Industrial Research Organisation in Australia (CSIRO), University of Adelaide, Texas A&M University, and Island Conservation (an NGO), the Safe Genes gene drive mouse effort includes a stakeholder engagement team of experts tasked with qualitatively assessing the questions, should we create this drive and, if so, under what conditions? The stakeholder engagement team is led by North Carolina State University, which has in turn partnered with Keystone Policy Center, Arizona State University, and the Expert & Citizen Assessment of Science and Technology (ECAST) network to design and conduct engagement activities.

This report summarizes the results of the first major task of the stakeholder engagement team: to analyze the landscape of stakeholder interests and perspectives surrounding the development of a gene drive mouse for biodiversity protection in island settings. This analysis will enable key feedback to the innovation teams and the Safe Genes program. The analysis will also help to inform future engagement strategies and activities for this effort.

Chapter 2: Methodology

Chapter 2: Methodology

2a. Online Landscape Analysis

An online landscape analysis was performed to review online articles and other publications that discuss genetic engineering and gene drives, particularly those related to the use of these technologies for biodiversity protection. This analysis informed the framing of stakeholder interview questions and identification of stakeholders to interview. The online landscape analysis also provided a point of comparison to evaluate whether the stakeholder interviews identified the salient themes of media coverage and online publications. This analysis was conducted through a variety of online searches using terms including conservation, environment, gene editing, invasive species, rodents, gene drives, islands, public health, and vector control. The searches resulted in a list of published online content, a list of relevant stakeholders (individuals that were referenced in those published items), and a list of organizations producing relevant content or referenced in other published content. The online searches did not cover every possible relevant search term or article; they typically only covered the top web search results and only included a combination of the terms listed above. To access peer reviewed scholarship, a search of Google Scholar was conducted using terms including gene drives, rodents and islands, but a comprehensive literature review of published scholarly research was beyond the scope of this task.

2b. Identification of Interviewees and Development of Interview Questions

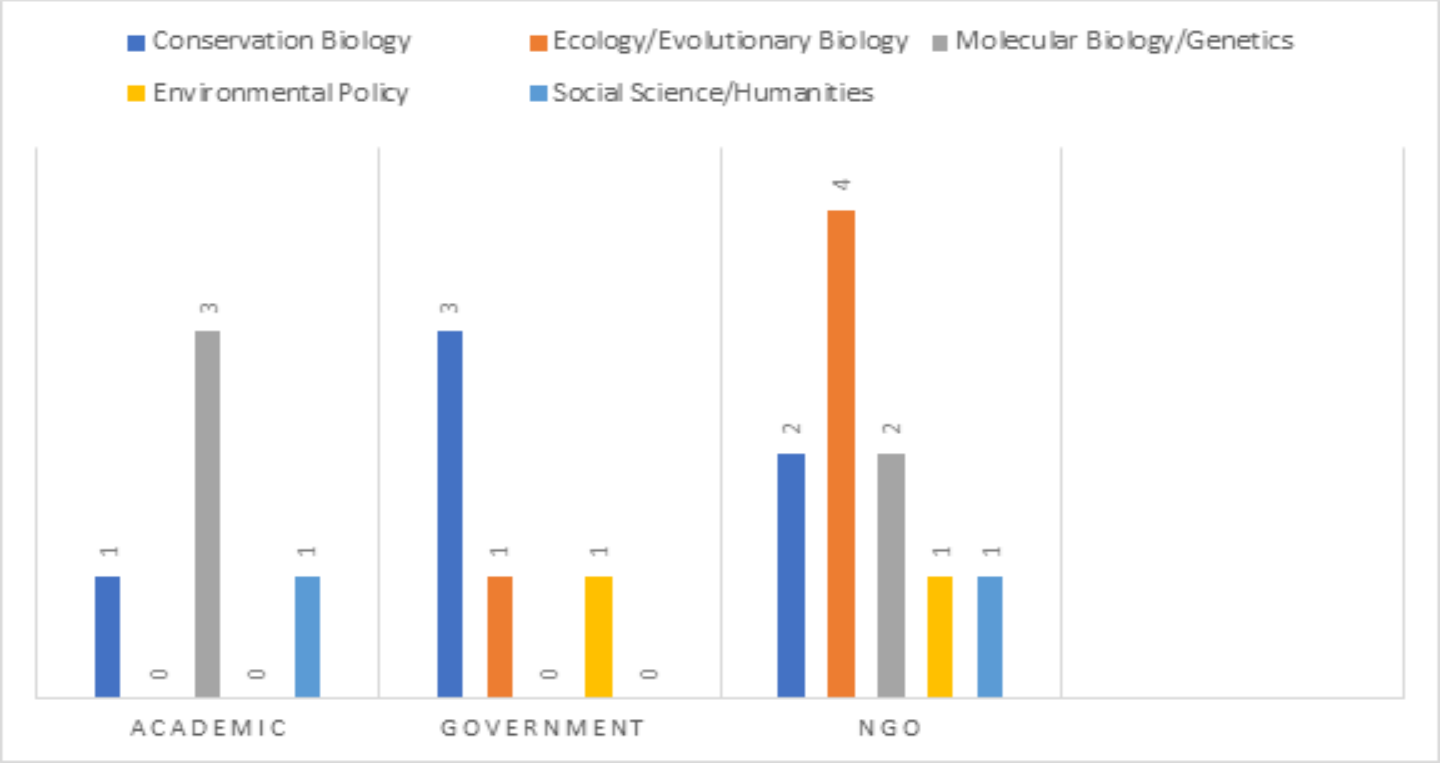
The online landscape analysis generated a list of key stakeholders, and this list was expanded by leveraging existing networks within the gene drive community (including the NCSU Safe Genes team) to identify additional potential interviewees. Individuals were identified within and across broad categories of overlapping interest and experience in (a) Gene Editing and/or (b) Environment/Biodiversity. Some individuals also had overlapping experience in (c) Agriculture/Food, and/or (d) Public Health. Interviewees included different institutional sectors (government, non-government, academia, etc.), levels of governance (local, regional, national, etc.), functional role (funding, research, advocacy, etc.), and perspectives (for, against, neutral). In choosing candidates for interviews, the team focused on capturing differentiating characteristics within an issue space. Some stakeholders had a depth of experience with multiple topics; others were more focused in one area or another. Those interviewed were not intended to be quantitatively representative of specific positions or interests; rather, they were meant to qualitatively reflect a diversity of perspectives. Twenty individuals – none from the NCSU Safe Genes team – were ultimately interviewed. To protect participant privacy and confidentiality, the names and organizations of the interviewees are not included in this report. This landscape analysis approach was reviewed by the coordinator for the North Carolina State University Institutional Review Board (IRB), who determined that the project activities did not constitute Human Subjects Research (HSR) as defined by federal regulations, and as such did not require Institutional Review Board review.

During interviews, the research team collected a limited amount of demographics data about the respondents, mainly concerning their professional roles and training, and geographic contexts within which they operated. Respondents mainly held professional roles as research scientists, administrative directors, or project managers either in the sectors of government, academics/research, or NGOs. Most organizations were national level or international level organizations, save for a few respondents who worked for local universities or NGOs. Most respondents reported that they worked either within a United States/North American or global context, with a few who worked in the New Zealand context. The vast majority of respondents reported living in the United States. Disciplinary trainings varied extensively within the life and environmental sciences, with the most common being in conservation

biology and ecology. Only a few respondents said they had training in the social sciences, and even fewer mentioned explicit training in policy. Figure 2, below, summarizes the sectors and disciplinary training of the interviewees.

Interview questions were developed to solicit information on participant attitudes on key issues, perceived risks and benefits of gene drive mice, and perspectives on engagement and governance. Interview questions are included in the Appendix.

Figure 2. Sector and Disciplinary Training of Respondents



2c. Conducting interviews and Analyzing Results

Interviews were audio recorded for accuracy purposes, and written notes were taken during the interviews. Partial transcriptions of the interviews were completed, and the interviews were then analyzed through the coding software Dedoose. Through Dedoose, a summary of all responses to each interview question was compiled, as well as other relevant responses to that question that may have been addressed in other questions. After relevant answers were compiled for each question, the questions were analyzed by the stakeholder engagement team, resulting in the identification of key insights, questions, perspectives, and quotes that were synthesized into a summary of results. The summary of results represents the synthesis of the stakeholder engagement team and **should in no way be interpreted as the consensus views or majority views of interview respondents.** Because of the relatively small number of stakeholders interviewed and the focus on diversity rather than numeric representation across various attributes, the analysis of interviews does not offer rigorous statistical claims nor quantitative assessment (e.g., % of respondents with specific views) but instead focuses on the diversity of issues, interests, and values discussed.

Chapter 3: Summary Results of the Landscape Anlaysis and Stakeholder Interviews

Chapter 3: Summary Results of the Landscape Anlaysis and Stakeholder Interviews

This section summarizes the feedback provided by interview respondents on questions regarding: a) participant attitudes toward biodiversity protection, gene editing and gene drives; b) benefits and risks of gene drives for invasive rodent control; c) sources of trustworthy information; d) engagement experience and perspectives; and e) understandings of governance frameworks that gene drive rodents might face. The summary groups responses thematically and presents illustrative quotes from interviews.

3a. Participant Attitudes

Prior to specific questions regarding gene drives for invasive rodents and island biodiversity protection, each respondent was asked about his/her attitudes towards biodiversity protection, gene editing and gene drives. Each participant was asked about any differences between his/her individual and institutional views and whether s/he believed that control/eradication of invasive rodents on islands is an important biodiversity objective. Most of the issues brought up in response to the attitudinal questions were further elaborated and expanded upon in response to the interview questions that dealt more specifically with the issues of benefits, risks, trust, transparency and governance, which are covered in sections 4b and 4c of this report. Hence, presented here is a high-level summary of some of the general attitudes.

Collectively and to various degrees, all respondents were concerned about losing ground to invasive species; extinction of threatened and endangered species; impact on flora and fauna and effect on biodiversity, public health, and economy; and the control or eradication of invasive rodents as an important objective. For example, one stakeholder said, "We are losing a lot of ground to invasive species and basically losing ground in general to threatened and endangered species becoming closer to going extinct. I think that we need to look at every available tool out there to be able to save these wonderful species."

The differences of opinion began to emerge when discussing what kind of tools are to be used and whether they should be derived from sources internal or external to the affected communities – e.g., whether they should be dependent upon community knowledge and practices and/or scientific discoveries and technological innovations. Related to the issue of what kind of tools to use were concerns over who would develop and determine the tools; these questions included not only discussion of the role of conservation practitioners, community stakeholders and scientists, but also discussion of different types of scientists. One stakeholder commented, "If conservation biologists aren't the ones with their hands in the pot trying to figure out what is positive and what is negative about it, then someone else is going to do it, and we might have the consequences that we're afraid of."

Some respondents expressed cautious optimism about the promise and potential of developing gene drives that are safe and cost-effective. Some were skeptical given past history of either failed attempts at population control or failure to exercise transparency with respect to other biotechnology applications. For example, a stakeholder commented, "A lot of that [opposition] stems from the seed crop corporations that have moved in…and are doing a lot of field trials with crops. There has been a lot of pushback because they haven't been as transparent with their pesticide use."

As a result, there were divergent views about the rate, direction and character of tools development, whether research needed to speed up to beat the ticking extinction clock; slow down to address knowledge, public understanding, and public engagement gaps; pause to have the regulatory safeguards in place; or stop altogether.

3b. Benefits and Risks

Overview: Benefits and Risks

Interviewees were asked about the perceived benefits of eradicating rodents on islands through the use of gene drives. The following themes and insights emerged:

- As compared to traditional invasive rodent control methods to protect and restore biodiversity, perceived benefits of gene drives include enhanced efficiency, efficacy, scalability, and cost-effectiveness– as well as reduced non-target impacts. But for some, the risks and unknowns of gene drives mean there are no comparative benefits at this time.
- Risks of gene drives for invasive rodent control include lack of efficacy, off-target gene transfer, the ability of the technology to spread beyond the small geographical context typically targeted by traditional rodent control methods, other ecosystem impacts, lack of social acceptance, and adaptation of gene drive technology for unethical and malicious uses. Another key risk with gene drives is the inability to identify and assess all the risks associated with their use.
- Interviewees discussed that gene drives could increase social acceptance as compared to other eradication technologies … or they could increase public backlash. Whether social acceptance is a desired outcome or not is dependent on perceptions of the other potential risks and benefits.
- Gene drives may provide a 'tool in the toolbox' for rodent eradications that offers advantages in certain contexts; however, it is difficult to compare a technology that is not yet proven and that may carry broader societal implications than traditional eradication methods.

Potential benefits of gene drives for invasive rodent control

As compared to traditional invasive rodent control methods to protect and restore biodiversity, perceived benefits of gene drives include enhanced efficiency, efficacy, scalability, and cost-effectiveness – as well as reduced non-target impacts. But for some, the risks and unknowns of gene drives mean there are no comparative benefits at this time.

Biodiversity benefits of eradicating rodents on islands

"We are losing a lot of ground to invasive species and basically losing ground in general to threatened and endangered species becoming closer to going extinct. I think that we need to look at every available tool out there to be able to save these wonderful species."

Interviewees referenced the overarching benefits of eradicating rodents on islands, including the restoration of bird populations, benefits to rare and endangered species, and benefits to general biodiversity. Therefore, interviewees reasoned, if gene drives are effective in the eradication of rodents, the biodiversity benefits of this eradication apply to gene drives as well. A few discussed that the benefits of eradicating rodents on islands was worth the cost, time, and effort regardless of which eradication methods are used.

Interviewees generally did not discuss the biodiversity benefits of gene drives at length. Rather, they primarily focused on the benefits of gene drives in eradicating rodents as compared to other methods of eradication like traps or rodenticides.

Efficiency, efficacy, scalability, and cost-effectiveness

> *"With our current tool set, we cannot afford to pursue [our] goals. We are looking to decrease the cost of scaling up best management practices."*

Interviewees discussed the efficiency and efficacy benefits of gene drives (in a general sense)—including the speed of application and impact, the duration of effectiveness, reduction in the need for monitoring efforts, and increased ability to respond to the spread of invasive rodents. With gene drives, users could in theory rapidly apply the tool, have a lasting impact, be able to respond faster in the case of reintroduction, and as a result be able to reduce management and monitoring efforts. Gene drives could reduce the number of steps required to be an effective eradication tool as compared to existing techniques, with potentially less travel, distribution of the method in question, and less management required. Some interviewees also referenced the potential to access areas with a gene drive that previously could not have been accessed with traditional methods, resulting in better efficacy of eradication. Ultimately, some interviewees viewed gene drives as a potentially cost-effective way to reduce the human and financial capital investments in invasive rodent eradications. Many interviewees referenced the fact that conservationists currently have the tools necessary (e.g., rodenticides) to eradicate invasive species on almost any landscape but that the costs in term of money, time, and personnel are significant.

As one participant said, "for work out…on islands, some of these islands are remote: they require a 5-day boat ride out there because they don't have an airfield. The ones that do have an airfield, they don't have consistent visitation…. Not to say that monitoring wouldn't be involved with gene drives. I just think it is significantly different and wouldn't necessarily need to be as frequent."

Some interviewees also discussed that the potential for reduced capital requirements through gene drives could enable scaling up current invasive eradication efforts and apply them to more islands, more difficult geographies to reach, and larger landscapes. One interviewee referenced it as a "landscape-scale solution" and another reflected, "with our current tool set, we cannot afford to pursue [our] goals. We are looking to decrease the cost of scaling up best management practices."

Interviewees discussed comparative benefits of efficiency, efficacy and cost-effectiveness in the context of implementation of gene drives vs. other eradication tools. However, they did not discuss the comparative efficiency and costs of gene drive development. One interviewee did note, "I think the benefits are [available] once you get over the technological hurdle of actually developing the gene drive." The same interviewee, however, worried that benefits for biodiversity-only applications may be harder to come by, and that a lot of these tools will be "developed for agriculture or for public health and it stops there."

Reduction of non-target impacts of rodenticide use

> *"The benefit is not in the eradication and action because we can do that now. It is in elimination of the non-target risks associated with the action."*

One of the other significant benefits discussed by interviewees is the species-specificity theoretically offered by gene drives and, by extension, the possibility of reduction of non-target impacts. Interviewees discussed that because gene drives are theoretically confined to one species, they are less risky to other species in the landscape. Because the method typically used currently for eradications is rodenticides, replacing them with gene drives would result in a decrease of the negative impacts of rodenticides. It would reduce the amount of toxicant used in an eradication, therefore reducing the number of non-target species killed and the amount of toxicant

entering the environment. Rodenticides have both known and increasingly unknown ecological impacts, said one interviewee, so the benefits of using gene drives would be to eliminate those impacts.

As one interviewee commented, "Right now, we have in theory the tools to eradicate rodents from pretty much any island landscape. It is just that the tools aren't ideal. Using second generation rodenticides…the risks are insurmountable: risk to [pets], humans, and other wildlife. We can't go there because of those risks. The gene drive tool provides us the same potential outcome as above without any of the risks. At least that is the promise. The benefit is not in the eradication and action because we can do that now. It is in elimination of the non-target risks associated with the action."

Another commented, "I think that the idea of being able to do eradications without extremely toxic rodenticides, which we are learning are incredibly potent and leave a lasting impact, would be an amazing thing."

No benefits

"There is no data to suggest any benefits; that is all hypothetical…The potential risks are too significant to explore the use of gene drives currently."

Some interviewees felt that gene drives had no benefits because their risks were too great. Some interviewees also noted that there are currently no real-world data behind the efficacy and cost-effectiveness of gene drives and that any potential benefits are theoretical. As one said, "There is no data to suggest any benefits; that is all hypothetical…The potential risks are too significant to explore the use of gene drives currently."

Potential risks of gene drives for invasive rodent control

Risks of gene drives for invasive rodent control include lack of efficacy, off-target gene transfer, the ability of the technology to spread beyond the small geographical context typically targeted by traditional rodent control methods, other ecosystem impacts, lack of social acceptance, and adaptation of gene drive technology for unethical and malicious uses. Another key risk with gene drives is the inability to identify and assess all the risks associated with their use.

Lack of efficacy

"There's dramatic propensity for wild populations to overcome genetic challenges."

Interviewees were asked about the perceived risks of eradicating rodents on islands with gene drives. Some interviewees identified the risk that gene drives would not actually be effective at eradicating rodents. Some questioned whether gene drives would actually access all subpopulations in an area on a timeline that was useful. As one interviewee reflected, "Would they be able to access all areas of the island? Would they be able to reach and interbreed on every part of the island? How long would it take?"

Others questioned the effectiveness of the gene drive itself. Whether through mutations that erode the efficiency of the drive, the emergence of resistance in the population, or the inability to develop long-term viable drives in populations, there is a risk that the drive will not work in the population in question. "There's dramatic propensity for wild populations to overcome genetic challenges," said one interviewee. Along with the risk that gene drives do not work is the risk of wasted money, time, and energy on developing this technology.

Non-target population gene transfer and other ecosystem risks

> *"But what if a mouse with gene drives gets off the island, as they got on there in the first place, and they go extinct? And it's hard to weigh, too. Are five species of crickets worth more than one species of mice? Who makes that decision?"*
>
> *"[Humans have had a] history of issues in conservation with misguided attempts at population control."*

There were also significant questions raised regarding off-target impacts of gene drives. Whereas interviewees discussed the benefits of reducing the off-target impacts of rodenticides to other species within the same geographical area, concerns over off-target impacts of gene drives focused on the risk of impacting the same species, or similar species, across a wide geographical area. Interviewees discussed risks of the gene drive spreading to a new geographical area: for example, going from an island to the mainland or another island.

One interviewee described rodents as "well-traveled" and suggested that there is a significant chance that they escape the confinement of an island. A few participants suggested that because of their inability to be contained, gene drives pose a significant ecological risk in their current form as they could cause rodent populations to go extinct in areas where they are native.

Interviewees also discussed broader ecological risks. Some interviewees mentioned the risk of horizontal gene transfer: that is, a gene drive could mutate and jump to other species aside from the target one and begin impacting those non-target species. Further, if the native ecosystem has become dependent on the invasive species, whether through being a food source, an important pest suppressor, or something else, then eradicating the rodents could have negative consequences on the native environment. One respondent referenced historical attempts at pest control by saying, "[humans have had a] history of issues in conservation with misguided attempts at population control."

Interviewees discussed the challenge of assessing risks of ecological trade-offs. As one interviewee said, "are five species of crickets worth more than one species of mice? Who makes that decision?" And as another interviewee said, "is the cost worth the potential losses on islands? So if you lose 50 bald eagles, is that worth the success of having the rodents gone?"

Finally, another risk discussed was that of irreversibility: once a gene drive is released, it may be irreversible in the ecosystem or ecosystems it is released in, as well as in non-target populations that it may escape to. Interviewees said that demonstrating control of the gene drive is important for addressing these risks.

The unknown unknowns

> *"There [is] a lot of concern around all the unknowns and the feasibility of developing the techniques …*
> *as it seems very, very experimental."*

Related to both of the above risks (efficacy and non-target effects), interviewees expressed general concern over the experimental nature of gene drives; for example, one commented, "there [is] a lot of concern around all the unknowns and the feasibility of developing the techniques … as it seems very, very experimental."

Underscoring this, interviewees also discussed the human inability to perceive all the risks associated with gene drives, and that this is a risk in and of itself. At this point in development, there is a risk of the tool getting ahead of our complete understanding and our understanding of its consequences. As one interviewee said, "are there potentially any other

non-target impacts that we don't know about, or aren't even thinking about? There is a level of uncertainty and newness as [the technology] relates to mammals and how that might impact ecosystems." As another said, "if people or agencies or initiatives start utilizing the tool in situations where they are trying to protect species on the brink of extinction, yet don't know the full efficacy of the tool in that setting, we could set ourselves up for failure in terms of achieving the conservation benefit we want."

An interviewee cautioned that researchers must strive to identify and answer the complex and unknown questions: "There's always more that we can learn and more than we could study. I hesitate to appeal to complexity, because you can say that for anything, and at some point we have to decide, no, we're going to do this, or not. But, you know, the data should be in hand to say that at least this has been looked at and addressed."

Risks beyond questions of rodent control

> *"The assessment of this can't be just on the basis of 'is this the way to get rid of rodents on islands?' any more than if you wanted to use nuclear weapons to remove rodents from islands - I'm sure it would be very effective, but you really can't just talk about it in that narrow way."*

Interviewees expressed concern over risks associated with the use of gene drives for purposes other than rodent control. Interviewees discussed the possibility of illegal, unethical, and malicious use of gene drives, include the weaponization of the technology; for example, one interviewee said, "Currently the risks pose potentially irreversible threats to biodiversity, to national sovereignty, to peace if we're looking at potential uses for bioweapons, risks to food securities… and there are ethical, social, and environmental problems that are raised by the use of the gene drives." There was also concern that once the technology is developed, there is no going back as "once it is known to scientists in other countries, who have other priorities, you cannot put it back in the box." Given these risks, some interviewees emphasized that we don't know enough about the consequences to even dare develop the "hardware" for gene drives.

There was also commentary that the framing of the interview questions – specifically around invasive rodent control – was not broad enough to discuss all the potential risks. One interviewee emphasized a key risk as being "that this is ultimately not about controlling invasive rodents on islands…that this is about moving forward a very powerful platform of technology, and that trying to limit the discussion to a narrow use case, especially one that is opening up the field, is too narrow and misleading. The assessment of this can't be just on the basis of 'is this the way to get rid of rodents on islands?' any more than if you wanted to use nuclear weapons to remove rodents from islands - I'm sure it would be very effective, but you really can't just talk about it in that narrow way."

Potential risks and benefits regarding social acceptance and regulation of gene drives for invasive rodent control

Social acceptance will affect research funding, development, deployment and governance of gene drives. Interviewees discussed that gene drives could increase social acceptance as compared to other eradication technologies, or they could increase public backlash. Whether social acceptance is a desired outcome or not is dependent on perceptions of the other potential risks and benefits: those that see gene drives as worth pursuing will see social acceptance as good, while those concerned that gene drives are too risky will not.

Increasing social acceptance….?

> *"Is it easier to weed out invasive species by using something like a gene drive, where those animals just don't get born? ...Is that better than animals that are born and you then have to seek out and destroy?"*
>
> *"Being able to remove the whole putting toxicants in the environment is a huge benefit because we don't even have to engage in those conversations. The conversations that you would be focused on are the what if's."*

While interviewees discussed social engagement in subsequent parts of the interview (summarized in section 4e), many also referenced these in the context of risks and benefits. Importantly, whether social acceptance of gene drives is a desired outcome or not is dependent on an individual's perceptions of risks and benefits.

On the one hand, interviewees referenced that gene drives could reduce the social and legal resistance to eradications that are based on the impacts that rodenticides have on the landscape.

One interviewee discussed the association people have between non-target impacts and eradication projects, while another discussed the difficulty of gathering social support for multiple uses of rodenticides if a project doesn't succeed initially. Gene drives could offer the ability to circumvent that social opposition by reducing the off-target impacts and increasing effectiveness. One interviewee discussed the opportunity to shift the conversation: "…. people end up not trusting the science. I think being able to remove the whole putting toxicants in the environment is a huge benefit because we don't even have to engage in those conversations. The conversations that you would be focused on are the what if's."

Some interviewees also discussed the moral superiority of gene drives that simply prevent rodents from being born instead of having to seek them out and kill them. As one interviewee said, "Is it easier to weed out invasive species by using something like a gene drive, where those animals just don't get born? To me, is that better than animals that are born and you then have to seek out and destroy? Which seems like a more violent method for some reason." Similarly, an interviewee commented, "The idea of biasing the offspring towards males or females, which eventually will eradicate a population, is potentially exciting in a couple of ways. One, it removes populations without having to do direct casualties. That has a strong influence with the public…"

… Or increasing backlash?

> *"Any early failures will be regarded as global failures by society and there will be no willingness to experiment any further."*

On the other hand, interviewees also discussed that the possible risks described earlier could lead to public backlash against gene drives. An initial failure with gene drives could create disillusionment with the technology itself. Such backlash and/or disillusionment could lead to gene drives not being used; one interviewee commented, "Any early failures will be regarded as global failures by society and there will be no willingness to experiment any further." Importantly, an end to experimentation with or use of gene drives is a result that for some was a risk, while others concerned about gene drives saw as a positive outcome.

In response to and/or independent of public response, interviewees also identified the possibility that a slow regulatory system could take too long to approve gene drives, or that a moratorium on gene drives would block their development. Interviewees identified risks of this regulatory scenario including a waste of resources in the development of gene drives and, ultimately, loss of biodiversity due to continued impacts of invasive rodents; one said, "The biggest risk is that it takes forever to get

drives approved and we continue to lose more species because of the controversy." However, other interviewees identified these scenarios of delayed regulatory approvals – or no regulatory approval – as desired and beneficial to prevent the other risks of the technology that were described above.

Gene Drives versus Other Rodent Control Methods

Gene drives may provide a 'tool in the toolbox' for rodent eradications that offers advantages in certain contexts; however, it is difficult to compare a technology that is not yet proven and that may carry broader societal implications than traditional eradication methods.

A 'tool in the toolbox'

> *"Like many things, it's another potential tool in the tool box that we can use. It doesn't have to be mutually exclusive with other technologies that have already been tried."*

Participants were asked about how the gene drive eradication method compared to other methods, like traps and rodenticides. Much of the discussion on risks and benefits (above) included comparisons to other methods of eradication – this included discussion of the possible benefits of increased efficiency, efficacy, cost-effectiveness, and scalability as well as reducing the off-target impacts of rodenticides. It also included discussion of the possible risks of unknown efficacy and impacts on non-target, native populations of rodents.

Interviewees discussed that gene drives potentially offer a 'tool in the toolbox' for rodent eradications and could be used in tandem with other eradication methods. The use of gene drives would not have to be mutually exclusive with the use of other techniques. Some interviewees felt that gene drives and other methods, like traps and poisoning, had different risks and benefits and could therefore complement each other. Therefore, which tool to use was dependent on the context and landscape.

'There is no comparison'

> *"At the moment, there is no comparison because it doesn't exist."*

Interviewees discussed that gene drives are difficult or even impossible to compare to other methods because they are so new and there are so many unknowns; as one said, "At the moment, there is no comparison because it doesn't exist." Interviewees also discussed the lack of understanding of the process that would govern the use of gene drives as well as the steps that users would have to take to use them. "The outstanding risks and concerns are so great and the potential benefits are so hypothetical," another interviewee said, "that to be able to compare and contrast them seems like a question that I can't answer."

Others emphasized that there is a wider set of implications and concerns associated with gene drives– such as biosecurity, food safety, and ecosystem health—than with other rodent control technologies. An interviewee remarked that gene drives represent "a very different kind of platform than other control technologies, [with] deeper existing questions of safety and stability when bringing this type of technology into a context of ecological conservation."

3c. Scenarios for gene drive use for rodent eradication

Overview: Scenarios for gene drive use for rodent eradication

Participants were asked about various scenarios in which gene drives could be developed and/or tested, including whether the island was inhabited or not, how remote it was, whether the drive was transgenic or not, and the physical geography of the island. Insights and themes that emerged included:

- Interviewees saw varying benefits and risks in various scenarios, often distinguishing technical considerations from social and regulatory considerations.
- Some felt that when viewed from a conservation perspective, eradicating invasive rodents using gene drives posed the same risks and benefits regardless of the physical landscape, whether the island was inhabited or not, how remote it was, and whether the gene drive was transgenic or not.
- Interviewees often remarked that piloting on remote, uninhabited islands with a simple landscape using a non-transgenic gene drive would offer a starting point that would be more socially acceptable and provide a better chance for technical success.
- Others felt that the scenario did not matter because there is no safe way to experiment with gene drives in the wild. Some interviewees discussed that they did not feel the technical constructs were ready for testing yet, regardless of scenario, and that they viewed island testing as years away.

Inhabited vs. Uninhabited Islands

"Application of this tool on inhabited islands from [the] ecological-social perspective is extremely challenging, at least initially, until it becomes bread and butter."

If your goal is a healthy biodiversity and mix of species, then I think all of these risks are the same."

Some participants did not see any difference in risks and benefits when comparing gene drive use for rodent control on inhabited vs. uninhabited islands. When considering the risks and benefits from a conservation perspective, many felt that there was no difference whether humans were present or not. One interviewee reflected, "If you are doing this for conservation I don't think it matters if people are there or not. If your goal is a healthy biodiversity and mix of species, then I think all of these risks are the same." Others noted the importance of species-specificity; for example, one said, "Intrinsically it sounds less risky on uninhabited islands, but if there is species-specificity, it might not matter." On the other hand, some discussed that the potential risks of gene drives for biodiversity are present irrespective of human habitation of the island.

Others discussed, however, that habitation matters more if the gene drive doesn't work: for example, one participant said, "If this works, I don't see why it matters, if humans are present or not. But if it doesn't work, then it might matter. Until the technology is proven, it does matter to some extent during the testing phase, but once the technology is proven, then I don't think it matters." Others felt that while the risks may appear the same, the risk profile is not very well understood so there could be unknown risks.

Interviewees also discussed risks and benefits to humans in the context of inhabited islands. An interviewee felt that humans could stand to benefit from the eradication work so there could be potential human-specific benefits to working in inhabited areas. Another mentioned that there must be assurance that

humans could not be harmed by a gene drive.

Other interviewees discussed that pursuing gene drives for rodent control on inhabited islands posed risks and complexities for efficacy not present on uninhabited islands. Some felt that it posed a risk to the efficacy of the work. With humans present, the projects have to consider biosecurity concerns resulting from purposeful and/or non-purposeful transportation of the rodents, either by re-introducing invasive rodents to the island or by transporting gene drive rodents to other locations. In addition, working on an uninhabited island may provide fewer barriers for following up a gene drive eradication with other traditional methods to ensure a successful project.

Others focused on social and regulatory considerations, with some noting that working on an inhabited island would increase requirements to engage, consult, and communicate with citizens of the island. While it may not impact ecological risks and benefits, the engagement process does impact the dynamic of the project and whether it proceeds. One participant discussed that the perception of risk is usually a bigger hurdle to clear than the "reality" of risk. Working on inhabited islands also may require a much stricter regulatory process, and the project's regulatory approval, at least to some degree, becomes dependent on public perception. Uninhabited islands, for the most part, may not have to deal with this degree of complexity. However, there were some that felt that community consultation and governance were important, regardless of habitation.

Interviewees discussed that testing gene drives first on uninhabited islands provides a way to build confidence around gene drives. Interviewees suggested that beginning on uninhabited islands was necessary to show the efficacy of the technology, demonstrate the benefits and risks, and build the confidence of the public in gene drive eradications. It would offer a phased approach to gain acceptance to then scale up. As one individual said, "application of this tool on inhabited islands from [the] ecological-social perspective is extremely challenging, at least initially, until it becomes bread and butter."

Remoteness of the Island

"There's no such thing as containment, whether it's an island that's far away or a place that is closed-in. Even islands that are in the middle of the ocean. There's no such thing as containment in this day and age."

"To have an extremely remote island, either way, whatever island you're dealing with, we're going to want triple safeguards in place."

Some interviewees felt that from an ecological risk-benefit perspective, if gene drives worked the way they are designed to, it would not matter how remote the island was.

Interviewees discussed biosecurity with respect to remoteness. Remote islands might be more bio-secure with a lower chance of escape of a gene drive mouse (potentially causing biological harm elsewhere) or re-introduction of the invasive rodent (therefore negating any of the benefits of the work). However, other interviewees emphasized the need for biosecurity even on remote islands; one commented, "to have an extremely remote island, either way, whatever island you're dealing with, we're going to want triple safeguards in place." Another emphasized that containment is impossible regardless of remoteness: "There's no such thing as containment, whether it's an island that's far away or a place that is closed-in. Even islands that are in the middle of the ocean. There's no such thing as containment in this day and age."

Interviewees also discussed that to reduce the risk of a gene drive spreading beyond an island, projects should consider more than just physical remoteness. Physical remoteness may be related to genetic remoteness, but there could be more gene flow to and from a remote island than one might expect, for example, due to human travel. It was

recommended that this gene flow be considered, as well as how far the species with the gene drive is from the native population.

Interviewees also discussed feasibility with respect to remoteness. Islands closer to the mainland could be easier to work on due to easier access, response time, etc., whereas remote islands could be costlier to work on due to increased travel, management, and other costs. Another felt that while traditional eradication methods made it more difficult to work on remote islands, the benefit to gene drives would be that it would reduce the cost of working on more remote islands through less human labor, management, and other costs.

Interviewees also discussed that using gene drives on more remote islands could carry less social risks. Islands that are more remote may avoid public attention and therefore be less likely to encounter public resistance to trials. In addition, remote islands can provide the perception of more biosecurity, thus reducing fears of off-island impact and increasing willingness to allow testing to occur. However, it was noted that regardless of the remoteness, those who are concerned about the use of gene drives and biosecurity will be aware of and engaged in providing feedback on their use.

Some felt that remote islands were beneficial because they offered an opportunity, like uninhabited islands, to build confidence toward future efforts to scale up. For example, one commented, "For a field trial, the remoteness of an island would give people less apprehension of an off-island impact. But for deployment, it's less of an issue. Once we get to the point where the deployment has reached social acceptance, the remoteness will not be a big deal."

Transgenic gene drives

"It's a manipulation regardless. It feels better if it wasn't transgenic."

Some interviewees expressed uncertainty as to whether using a transgenic gene drive (containing genetic material from other organisms) mattered or not, and to what degree. Some said that it might matter, but not a lot.

Those that felt it mattered discussed the difference between the technical feasibility of using a transgenic gene drive and the social acceptability of doing so. In terms of feasibility, one interviewee raised the question as to whether it made the engineering process more difficult if the drive was transgenic. Other interviewees felt that the impacts of a transgenic gene drive should be evaluated more than the impacts of a non-transgenic gene drive because there are more unknowns around transgenics. Another noted that, depending on the species and the drive in question, it may have to be transgenic because there may not be the needed genes preexisting in the species.

Many comments focused on the social acceptability of a transgenic gene drive. Some said it would not matter if the gene drive was transgenic, and others said that while it did not matter to them, it might to some who do not like it on principle or who perceive a transgenic manipulation as riskier than a non-transgenic manipulation: "It's a manipulation regardless. It feels better if it wasn't transgenic." A social perception of higher risk, even if in fact there was not a higher ecological risk, could threaten the ability to use the gene drive. Accordingly, a non-transgenic gene drive may be more suitable as a first phase to build trust and confidence with the public; one interviewee said, "This is one of those questions that will disappear as a concern, between what is transgenic and what is cisgenic. For a field trial, maybe it's helpful not to be transgenic, that the optics may be easier for public engagement."

There was also some discussion over the question of whether the gene drive (transgenic or not) was introducing a new trait into the population. The gene itself may be from another species, but if it is simply modifying or amplifying an existing trait, it may be

perceived differently than if it adds a completely new trait to the organism.

Some interviewees expressed concern over the act of manipulating a genome regardless of whether it is transgenic or not. To them, the risk was in the act of creating a gene drive in the first place, and it thus did not matter whether it was done through using another species' genome or not. These interviewees felt the safety implications of gene drives are not known and should be dealt with accordingly, regardless of where the genes are coming from.

Physical geography of the island

"I think for a field trial, a highly diverse physical geography of an island will be harder to evaluate the penetration of the gene drive. However, the value of a gene drive in a complex geography of an island, that is when a gene drive would be most beneficial. To be able to get to rodents in far remote crevices of an island, that a rodenticide could never get to. To get to the last female that could be impregnated."

Some interviewees felt that the physical geography of the island did not matter and that the benefits and risks of using gene drives would theoretically be the same, regardless of the geography. Interviewees noted that one of the benefits of the gene drive is that it should ensure that the landscape is not a factor, as the effectiveness of the drive is guaranteed by mating. A gene drive would thus be able to penetrate areas that other conventional rodent control techniques would not be able to penetrate. For example, steep slopes limit the application of rodenticides and traps, but a gene drive could potentially overcome those issues.

One interviewee felt that the risks of gene drives were the same regardless of the landscape but the benefits—in terms of the effectiveness of the gene drive—could be changed or limited by the landscape, through the dispersal and spread of the gene drive, or lack thereof. Participants acknowledged that more complex landscapes would likely require more work and would ultimately increase the risk of project failure. Landscapes with complex micro-habitats and multiple ecological zones, patchy population structures, mountainous terrain, cliffs, or large water bodies would likely require more rodent introductions, maintenance, and monitoring to ensure that the gene drive has spread across the landscape and influenced all the rodent subpopulations. While more complex landscapes and populations would likely increase the effort required to complete an eradication, they would require less effort relative to other techniques. In addition, it was suggested that current technology, like drones or autonomous cars, would be able to distribute gene drive rodents across a wide variety of geographies.

Some interviewees discussed that beginning trials on a small island with simpler geography and smaller rodent populations was ideal. Working on a simpler landscape would also make it easier to follow up with other control methods as needed. Simpler landscapes may also be easier ecologically (as the project would likely have a greater success rate and chance of full dispersion of the gene drive) and socially (as people could potentially be more comfortable with a trial in that location, and because a higher likelihood of technical success would build confidence for future trials). By working on the island that gives the gene drive the greatest chance of success, there would be more opportunities to continue research and expand the application of gene drive work; as one interviewee said, "I think for a field trial, a highly diverse physical geography of an island will be harder to evaluate the penetration of the gene drive. However, the value of a gene drive in a complex geography of an island, that is when a gene drive would be most beneficial. To be able to get to rodents in far remote crevices of an island, that a rodenticide could never get to."

Some interviewees felt that potential trials shouldn't be happening regardless of the physical geography of the island. As one interviewee said, "it doesn't matter because, again, there is no safe way to experiment with these technologies in the wild."

3d. Sources of Trustworthy Information

Overview: Sources of Trustworthy Information

Interviews explored respondents' perspectives on trust in the field of gene drive rodents by asking them two separate questions – whom they trusted and didn't trust for information, and whom they thought citizens (i.e., laypersons) trusted and did not trust. Three primary insights emerged from an analysis of responses:

- Respondents tended to trust formal, expert sources for information, such as university researchers and government agencies, while perceiving citizens as primarily trusting friends, family, and local community networks. But categories were not absolute and varied across sectors of stakeholders. Table 1 summarizes trusted and not-trusted entities (without reporting frequencies of mentions).
- Themes of bias, conflict of interest, and transparency strongly influenced discussions of trust. No source of information was seen as categorically unbiased, with calls for transparency across sectors as a common precursor for trust.
- While the science of creating gene drive rodents may be abstract and disconnected from geographic contexts, many respondents emphasized the importance of involving local entities as trusted sources of information. This exposes a potential tension as research transitions from laboratory testing to environments where local knowledge and community trust may become paramount.

Table 1. Trust and perceptions of trust of information sources

**Table represents aggregate responses for each "Trust" and "Non-Trust" response category across the six most frequently mentioned information sources. An "X" represents one or more explicit mentions of the respective information source.*

Information Source	Trusted by respondents	Not trusted by respondents	Perceived trusted by citizens	Perceived non-trusted by citizens
Scientists	X		X	X
NGOs	X	X	X	X
Media		X	X	
Private Companies		X		X
Government Agencies	X			X
Interpersonal Networks			X	

Citizen Trust and Non-Trust

> *"People have their personal networks, and they seem to form opinions quickly based on what each other thinks. Citizens trust citizens very rapidly."*
>
> *"Even when scientists speak up openly and honestly, there is a perception of ulterior motives."*

Respondents were asked to give their perspectives on what entities they think citizens (i.e., laypersons) trust or do not trust when it comes to information on gene drive rodents. The most common response for "citizen trust" was that citizens place the most trust in their interpersonal networks. Specifically, citizens seek out the opinions and perspectives of their friends, family, and "thought leaders in their communities" and use those influences to form the basis of their perspectives. As one respondent said, "People have their personal networks, and they seem to form opinions quickly based on what each other thinks. Citizens trust citizens very rapidly." These responses suggest that further inquiry into the potential role of social media is warranted. Additionally, independent academics and researchers were commonly mentioned as trustworthy entities for citizens, specifically, "researchers with good reputations that don't have hidden agendas about doing their work. People would understand them to be trustable."

Some respondents believed that citizens lack trust in scientists (generally speaking), the government (including the military), and profit-driven private interests. Although scientists were also sometimes identified as a trustworthy source, respondents generally thought that public trust in science has diminished in recent times, especially trust in the science of genetic engineering. As one respondent put it, "Even when scientists speak up openly and honestly, there is a perception of ulterior motives." Local scientists and researchers were much more likely to be trusted sources of information than ones without place-based connections, especially those who held positions at universities rather than the government or private industry. Citizens do not seem to trust that the motivations for decision making across governmental and private companies reflect their best interests, or what is best for the environment. Lastly, citizens were perceived to trust news media to a relatively high degree, despite what the respondents identified as a tendency to misrepresent scientific facts.

Respondent Trust and Non-Trust

> *"I do not trust voices with strong commercial, military interest, and [am] concerned about voices that have an ideological interest in moving forward with biotech more generally."*

When asked whom *they* trusted most as sources of information about gene drives in mice for biodiversity protection, respondents reported academics and researchers more consistently than any other individual or entity. This was contrary to their perspectives on citizen trust and non-trust (described above). Specifically, many respondents explained that it was scientists who contributed to peer reviewed research, did not hold any commercial interests, and contributed to a "transparent dialogue" about the risks and benefits of gene drives. Very few respondents indicated that they trusted governmental agencies relative to independent researchers and scientists, and even fewer spoke of having trust in private sector entities and NGOs, who many viewed as biased and lacking the kind of objectivity and independence of an academic researcher.

Respondent non-trust perspectives were divided much more evenly across three main categories: trust in news media, commercial interests, and environmentally-oriented NGOs. News media were often categorized as inflammatory and politically motivated rather than promoting fact-based debates. The internet was specifically identified as a culprit in

exacerbating "hysteria" due to social media's ability to make "large sweeping statements that aren't based in facts." In similar fashion, some environmentally-oriented NGOs were deemed untrustworthy for displaying what one respondent specifically characterized as rabid "anti-science." More often though, respondents said NGOs were untrustworthy due to their special interest in either the success or failure of gene drive technology; as one respondent said, "Last (to trust) would be the private sector including NGOs where there is a mission benefit to the outcomes of these projects and there is also a financial benefit to the organizations for taking the projects on. Reputational benefit essentially...I know the integrity of an NGO-like [organization] but that doesn't erase the fact that they will benefit from the success of this tool."

Generally speaking, "science advocacy" was a major source of respondent non-trust beyond just NGOs. Several respondents said that, generally, uncritical viewpoints of gene drives are untrustworthy due to their downplaying of the high degrees of uncertainty and risk associated with gene drive interventions. One respondent indicated this to be a phenomenon of researchers who even appeared as "independent" and publishing in peer reviewed journals: "I think critically about whether their data actually shows what they say it's showing. So I would say the most [trust] would be peer reviewed articles or stuff that is presented in conferences, but taken with a grain of salt considering that they may or may not be overhyping this as something that they are really invested in." Additionally, this investment in gene drive technology is an especially potent concern for entities that have commercial or defense-related interests tied to the success of gene drives. As indicated by one respondent, "I do not trust voices with strong commercial, military interest, and [am] concerned about voices that have an ideological interest in moving forward with biotech more generally."

Transparency

"So just imagine the general public that has never taken a science class: they would have even more apprehension, I suspect, with something like this. It is going to be a situation where you have to go slowly and make sure that you educate and share and bring people along to build trust for both scientists and the public."

"I think as we move forward, if we can do many trials on small islands where you have contained populations, you can really understand what can happen and share that with the public and build confidence, build their trust, and build trust with other researchers. That is a great way to go."

Trust is intimately bound to the level of transparency across all aspects of development and implementation. The relationship between transparency and trust was a consistent theme brought up by respondents. Across all aspects of gene drive development and implementation, respondents placed high value in developing greater capacities for transparency to increase not only the trust that diverse publics have in decision making, but also the trust that stakeholders themselves have in gene drive research, policy, and implementation. Perhaps due to the demographics of the respondent base, particular focus was paid to transparency issues relative to the actions of governmental institutions as well as research and development.

Where governmental organizations are concerned, lack of transparency and diverse knowledge consideration can erode trust, which many respondents indicate was already in short supply for governmental agencies. As one respondent put it, "government experts are far down the list" when it comes to trustworthy sources of information and decision making. Another respondent said that, "I think that there are enough people that don't either trust [the government] or have just a bad taste of government altogether, that isn't going to necessarily be impactful to them."

This distrust of government seemed to be even more amplified when it came to projects funded by defense-related agencies, which may or may not have standards of transparency like other governmental agencies. Citizens can react to this lack of transparency by assuming harm is being done to either them or their communities, as one respondent in military-based conservation efforts reported; one interviewee commented, "Sometimes their [the public] problem is with the government and not our technique, even though we are not wrapped into that. In aerial rodenticides, people don't want the army spraying them. [They have a] preconceived notion that army sprays them with stuff, and that this is part of it, assuming the army is going to harm them. People don't think we are doing what we are actually doing."

For research and development, many respondents stressed the value of peer-reviewed data as trusted sources for new technology development and implementation. In addition, as one respondent put it, research "needs to be transparent, independent, be clearly defined on what the research is doing, and who it's funded by." Project funding was a particularly important point to be transparent about in research in order to build public trust; one respondent said, "People more and more are demanding full transparency and are following the money behind who is speaking. I think that at the end of the day, full transparency of any conflicts of interest is incredibly critical for people, particularly when it comes to biotech."

Should transparency efforts fall short, trust can erode quickly into what one respondent called a "science communication pollution" situation, where affected publics and stakeholders do not know whom to trust, and evidence-based decision making becomes very difficult. One interviewee said, "If this situation becomes a polluted science communication situation, then it will be very difficult to find anybody that most people will trust. That's the worry I have about the entire thing. That it will become that, and the evidence will no longer exist as an independent category." Concerns like this were echoed by another respondent, who elaborated on the precarious nature of advocating for genetic engineering interventions: "We see this over and over again, where the public, even the educated public, has huge amounts of distrust for the NGO communities, the government, anyone involved…national park services, any agencies involved in terms of killing animals on islands to try to restore other species. That's really going to be elevated with respect to talking about gene editing, gene drives."

Trust through Local Involvement

"When technology is developed outside, no matter what it is, there are always questions about the motive of the outside company or entity bringing that here, why they want to do that here, and what their intentions are. That is one of the reasons why we wanted to involve our local university in either the development [of the technology] or just working with the coordination to help validate that this is science-based."

Local entity involvement in gene drive development and implementation is key to developing trust in decision making because of the high level of trust individuals place in their interpersonal and communal networks. Respondents suggested that local "leaders in the field" would be more trustworthy than experts from outside entities. Further, friends and neighbors who work at local institutions, even ones not directly involved in technological development or implementation, can potentially function as important sources of trusted information and perspective. This is exemplified by one respondent who said, "I think that if I could talk to people about this project not as a scientist but as their children's biology teacher at a high school, I think they would trust me." One respondent suggested this to be a distinct characteristic of affected island communities, making public outreach more challenging: "I think that the island way is talking to your neighbors and other people you trust and getting their perspective on it. Which

doesn't necessarily mean they are given the correct or right answer. That is why work here is so difficult, because it is important for us to somehow reach out to whatever entities that those people value."

For some communities, trust and transparency issues are the product of previous experiences, particularly with respect to GMOs, where some of the debates about gene drives are being situated. Knowledge in these cases is seen as being controlled, as one respondent put it, "by corporations which then control the technology and profits." This poses an additional challenge for communities that have a history of unfavorable experience with GMOs; as one interviewee commented, "And a lot of that [opposition] stems from the seed crop corporations that have moved in … and are doing a lot of field trials with crops. There has been a lot of pushback because they haven't been as transparent with their pesticide use."

Reaching out to and linking to locally-valued entities during development and implementation can legitimate a technology in the eyes of communities. One respondent, sharing personal experience in a separate geographical context, pointed specifically to local universities as a trusted source of information in technological development and research: "I think they (the local community) tend to lean towards the universities to a degree. Not in all aspects but I know it plays different on islands. That is one of the reasons we wanted to fund work through [a university on an island]: it validates the technology [when] it is developed here and implemented here."

If local entities are left out of research, policy, and deployment processes, it is much more likely that the motives behind decision making will be perceived as not being aligned with the interests and values of local communities and institutions, exacerbating the lack of trust that already exists towards externally-funded gene drive projects.

3e. Engagement experience and perspectives

Overview: Engagement experience and perspectives

During interviews, respondents were asked about their experience with engagement with stakeholders, communities, and publics regarding issues related to biodiversity or genetic technologies. Because of the novelty of exploring gene drives in rodents, none of the respondents had experiences that mapped perfectly onto this project's challenges, but many respondents shared relevant perspectives and insights in the following categories: 1) risk perception, 2) respect and shared vulnerabilities, and 3) issue framing. Key insights and themes include:

- It is important to identify shared values, vulnerabilities, and perceived risks and benefits that exist within communities.
- It is important not to be too "pushy" about the issue and agenda that are the focus of engagement, especially if those facilitating engagement come from outside the community.
- It is important for community participants to feel like sharing their perspectives and opinions is influential as a "tool for actually determining an outcome" and that they are not serving a role of simply "checking off a box for community engagement."

Risk Perception

"As conservationists, we come in to each of these settings to say, 'protection of your native wildlife is the most important thing to us in the world and we need you to consider these conservation actions and the use of these tools to protect these bird species that have been globally recognized as endangered or critically endangered.' But the local communities may not share the primary sense of importance that we achieve from question-derived notions of conservation and resource management."

"Regardless of how much information, science, or background you provide, or how many concerns you address, some people and organizations will never be satisfied with any of the science. They are so opposed to certain methods that it is obvious that scientists are lying and being controlled and that they know there will be massive negative impacts even if there is no evidence of it. These strongly held opinions will never change."

Many of the respondents discussed the public's likely negative perception of gene drives. Some attributed this to misunderstandings about genetic engineering technologies, and a tendency to project negative perceptions of one technology onto another. As one respondent put it, "I think it is just an important conversation in that sense because it is clear to me that people lump things together, they don't separate them. For instance, there is a range of technology like transgenic, or whether you are just genetically modifying something, but it doesn't necessarily have a gene drive, and there is definitely a misperception of the range of tools that are within the genetic suite and even just biotechnologies in general."

Other respondents took a more nuanced view of the complexity of risk perceptions in an environment where publics and stakeholders are generally lacking trust. These risk perceptions are not necessarily mediated by levels of technical understanding, but by a more fundamental distrust in the control mechanisms around agricultural and environmental biotechnology, a distrust in the agendas of those facilitating the development of new applications, and a fear of negative unintended consequences. As one respondent put it, "The issues that commonly arise are about the unintended consequences. If we

don't have all the facts, maybe we shouldn't pursue anything. It's easy for scientists to think that they can provide enough facts, and that facts will change opinion. It's been clear to me, looking at what people value and what values they bring to the discussion are more important if not equally important."

Respondents also observed that publics tend to respond to the diverse array of genetic engineering technologies with concerns that assume negative unintended environmental and health consequences will occur as a result of application. As one respondent shared from their own experience: "It really depends on if they have already made up their mind. A lot of times people are just responding to me based on emotion. It's funny, I try to think about every interaction I have had, and the last one was basically 'no, you are not going to be able to do that.' They had made the decision that messing with genetics is bad and they weren't even open to exploring the conversation any more. I get the sense that most people will hear what I say but won't change their mind and beliefs because it is so grounded in there." Understanding how affected publics perceive risk and how they prioritize and categorize potential biodiversity solutions differently from experts is integral to designing and facilitating engagement that promotes inclusive decision making.

Respect and Shared Vulnerabilities

Many of our respondents acknowledged the importance of not dismissing concerns raised by citizens based on them being "unscientific." Respect towards the priorities of local communities was demonstrated by comments about how local community concerns differ from those of scientists. Scientists tend not to prioritize risks and benefits the same way as communities because they usually lack a sense of direct connectedness. Therefore, during engagement, it becomes very important to identify shared values and vulnerabilities that exist between project personnel and community members. Project agendas can then be based on these collective understandings. One respondent shared a personal example of how this process works:

"We started with the island community and we sat down with the community leaders about what was important to them. What did they like about it (the project)? What was important about the ecosystem, the sea birds, and the plants? Did they like rats? I can't think of them specifically, but we did identify common connectors and used those to structure our larger engagement with that community... [W]e got vulnerable with them and acknowledged their vulnerability and their concerns. And when community members said 'Hey, we are worried that your use of rodenticide will kill all the fish,' even though, as practitioners that have used these tools before, this is an extremely unlikely outcome, we say very honestly we are very worried about that too and don't want that to happen."

Respondents warned that if project researchers continuously prioritized their own values and desired outcomes and ignored those of local communities, they could encounter resistance in development and implementation. If, instead, engagement proceeds with respect and incorporates shared vulnerabilities, assessments of technological applications informed by local communities can significantly benefit biodiversity projects. As one respondent put it, "People have sophisticated ways of thinking about power, and who benefits, questions of control, and people bring experience from other experiences with conservation and powerful tech and bring that to

"Stakeholder engagement isn't [something where] they ask their questions and you give back the canned response, but that you actually take their concerns into account and reflect on them and feed that back into how you are doing your program."

"Science and facts and data don't play well in the community engagement sphere, at least not as your initial tool for engagement. What plays really well is the connectors: how do you connect with people and how do you enable them to see you as a human being and as someone who is just like them, which we all are ultimately."

bear in assessments of new tech...People assess in smart and intelligent ways and you actually have to talk with them about it."

Issue framing

Several respondents talked about issue framing as an important factor deserving careful attention for facilitating engagement. They said that public engagement around potential gene drive applications must present an agenda that reflects the values and interests of the local community. If the issue that gene drives seek to solve does not resonate with local audiences, it will be more difficult to facilitate inclusive decision making. As one respondent put it, "it's helpful, if possible, to be designing a more in-depth stakeholder process to talk to people across the spectrum, to say 'here are some of the questions we're thinking of asking. Are we missing something? Are there questions or a framework that you think should be incorporated somewhere in there?' So that way, as a participant, I'm not walking into a space that's been framed in a way where I don't even agree with the premise."

"The way you orient questions makes a difference for who can and can't participate. How you frame it will make people feel welcome in the space or set up for something they're not interested in."

"I would highly recommend making it (engagement) so that people can have a personal connection and can be involved and can guide the course of a technology."

Further, respondents said it was important not to be too "pushy" about the issue and agenda that are the focus of engagement, especially if those facilitating engagement come from outside the community. One respondent illustrated this through one of their engagement experiences: "I was cautioned to not have the attitude of 'I'm coming here from the outside and I know what's best and you need to listen to me.' I was cautioned very, very strongly to not take that approach, to be more passive, to wait to be invited, and then give an opinion and share an opinion… I don't want anyone to say we're working on this technology without telling people, and without engaging people, but I also don't want to be too pushy and forcing myself into these communication roles."

To avoid this pitfall, engagement programs should strive to establish local connections, allowing local communities access to the issue framing and agenda setting stages. This requires, as one respondent described, "engaging everyone that you can and engaging them as early as possible" in the development process of potential gene drive conservation solutions. In addition, it is important for participants to feel like sharing their perspectives and opinions is influential as a "tool for actually determining an outcome" and that they are not serving a role of simply "checking off a box for community engagement."

3f. Governance Frameworks

Overview: Governance Frameworks

Respondents were asked to share their perspectives on governing the different phases of gene drive development and implementation, specifically the phases of basic research, field trials, and environmental release. Below is discussion regarding each of these phases, followed by a more general discussion of scales of governance that transcend these developmental phases. Key themes and insights include:

- Regarding governance of laboratory research, some thought that no additional governance is needed, others emphasized the need for greater transparency in the research, and others called for a moratorium on laboratory research until additional governance is established.
- Regarding governance of field trials and environmental releases, the main issue was the significant amount of uncertainty of how gene drive modified organisms might behave beyond the laboratory. In response to this uncertainty, some discussed the need for an adaptive management approach while others emphasized a precautionary approach precluding environmental release.
- Respondents discussed the possible need to apply and build upon existing regulatory frameworks; this includes involving new entities not typically involved in governance decisions.
- Respondents discussed overlapping scales of governance and communicated many different views about how governance should proceed on what scale. They often emphasized the priority of one scale of governance over another, dependent on their opposition to or support of gene drives.
- Respondents discussed the importance of the 'transboundary nature of gene drives' and its implications for international governance.

"That's kind of a million-dollar question. Everyone is dealing with that, not only with gene drives and genome editing in general. On a broad level, the more governance the better, in terms of having a structured process on how decisions are made... Having transparency and having a transparent process where you have decisions that are made based on a prior-made framework, where you have triple safeguards, and if certain conditions aren't met, you have stop gaps in place. That framework would ideally be developed by multiple stakeholders on a consensus basis and be in place before the experiments were underway..."

Governance of Laboratory Research

"In my opinion, and maybe this is just me being optimistic, I think having research community norms and guidelines about how to conduct the research is sufficient... I think in most cases [it is sufficient in] small research communities, where most people working on this know each other and are funded by the same organizations, and I think the organizations that fund them have the power to enforce best practices...for the most part, having those norms and guidelines in place and then either voluntarily following those rules or having the donor agencies enforce them, I think, is fine for research in the lab. But I do think there also needs to be clear explanations to the public about what is going on."

"There should be very clearly delineated international regulations that will prioritize the protection of the environment and food regulations and people. Only after these regulations are firmly in place at the international level, should we assess if a process for independent scientific assessment and regulatory oversight and commercial control is even possible to protect people and the planet. I think that goes for people in the lab; these are important steps to take ahead of any development of the hardware even for in the lab."

Respondent perspectives on governance of laboratory research fell into three general categories. First, there were those that did not think any special governance considerations had to be made for conducting laboratory research with gene drives. If lab protocols are conducted in a safe and cautious manner, with a little more "scrutiny on biocontainment, to a level that probably needs to be tightened up or at least ensured it is up to standard," no governance actions beyond those applied through existing institutional mechanisms or similar frameworks were necessary.

Another set of respondents were aligned with this thinking but called for more transparency in basic research. Full disclosure of research results, protocols, and funding were seen by them as critical to making informed governance decisions around gene drive applications; therefore, additional mechanisms requiring full transparency should be built into all gene drive related laboratory research.

Finally, there was a set of respondents who did not think any laboratory research should be conducted until all governance issues related to gene drive conservation applications were hashed out and settled. Some of these respondents explicitly called for a moratorium on gene drive research, specifically on the decision to construct and experiment with functioning gene drive organisms in the laboratory. From their perspective, only after robust regulations have been collectively constructed around the potential commercial and environmental applications of gene drives should laboratory work be pursued. In addition, they called for enhanced containment and personal biosafety protocols to be incorporated into the laboratory setting before gene drive research continues, to prevent accidents and improve security oversight.

Governance of Field Trials and Environmental Release

[Responding to a question about field trials] "That is something that we are working through because there are no guidelines except for guidelines that all of the stakeholders make up themselves."

"Then we should build the experimental settings up with larger (but enclosed) areas and simulations and then eventually try an easily-controlled field application where we could test rodent success in achieving what we want. It would also answer questions like what other species were impacted? What implications are there? Did any escape? What did project look like? Most people and scientists will trust the data that is there and the results that are there."

Due to the early stage of laboratory research, and the lack of precedent for governing a genetically engineered organism that could spread through a population at super-Mendelian rates, most respondents did not have a clear sense of how to move forward with the governance of field trials and environmental releases (Note: the Safe Genes program does not fund activities that involve environmental releases). The main issue was the significant amount of uncertainty of how gene drive modified organisms might behave beyond the laboratory. Risks involved with environmental experimentation are not well understood, unintended consequences are difficult to predict, and the technology may not be fully reversible.

Respondents recognized high degrees of uncertainty within the current state of gene drive development but diverged in how to address these issues. Some believed that the best course of action is one of careful experimentation through highly monitored and regulated field trials on remote islands, where the chances of escape are minimized. As one respondent suggested, "I would choose a small island with a small population that doesn't have too complex an ecology around it. Just do some experimentation with populations like that first, before going to bigger populations that might have more complex issues, such as ...human habitation, remoteness, and geography." From this perspective, the way to understand and mitigate unforeseen circumstances is to encounter them and respond accordingly through a process of adaptive management.

Other respondents stated that no experimentation should be pursued until robust governance mechanisms are put into place to regulate gene drive applications. For them, taking a precautionary approach is the best way to avoid harmful, unforeseen consequences and plan for their mitigation before they materialize. Relatedly, there were a few respondents who probed the question of whether the uncertainty surrounding gene drive applications could ever be mitigated to a level where it was safe and morally acceptable to be pursued. For them, no amount of precautionary policymaking or adaptive management practice can make gene drive applications a viable option, as indicated by one respondent: "... putting a gene drive into the wild is not an experiment. It's a dangerous manipulation of an ecosystem with an infinite number of unforeseen consequences. We can't afford to be experimenting with gene drives that have such irreversible and dangerous implications, particularly without full understanding of long-term impacts on our health, the environment, and livelihoods."

Scales of Governance

Many challenges exist in thinking through and constructing a governance system for gene drives as they move from laboratories to field trials to environmental releases, as described above. An important theme that emerged was the overlapping scales of governance, ranging from the local to the national to the international. Importantly, these themes do not map perfectly onto the phases of experimentation and release, with some respondents, for example, emphasizing the necessity of international governance regimes for laboratory research.

Local Level Governance

"You have to start with the local population, whatever is local outside unpopulated islands. [It] inherently takes time for people to argue back and forth about different opinions, and then ultimately it's the government of that particular island that would need to decide with contributions from people who are experts, and people who live and could be locally affected by the field trial."

"I think in terms, as far as the governance for moving things into the field, if I was to point to the World Health Organization framework of looking at genetically modified mosquitoes, I think how it is spelled out in there is appropriate. It is crucial and very important to get the local authorization to do these tools. I say it slowly because I think of how difficult it is if you look at the landscape as a patchwork and how to get various communities supportive."

Many respondents who prioritized field trials and release as the main governance challenges associated with gene drives focused on local level governance mechanisms as the main structures for decision making, emphasizing that communities should be engaged in decision making for field trials and release. Communities situated closest to the area of application should be engaged and consulted in decision making; if a potentially affected community decides it does not want to deal with the uncertainty and potential risks of gene drive applications, they can opt out of being subjected to them.

National Level Governance

> *"Overall, the regulatory system is not yet aligned with the technology that is being developed."*

Respondents generally recognized the importance of applying existing frameworks for biotechnology regulation, such as the U.S. Coordinated Framework for the Regulation of Biotechnology, to gene drives. However, many respondents also raised concerns about the adequacy of such frameworks to govern gene drives, whose designed effects and potential unintended consequences may not map perfectly on to the history of biotechnology products. Therefore, it may be necessary to incorporate national level agencies not previously involved in the governance of biotechnology. One respondent spoke of the potential challenges: "The products of biotechnology are governed in bizarre ways through the Coordinated Framework. There isn't clarity in how different agencies interact and who governs what. For example, for control of a modified invasive species on an island, it is not clear to me which agency would be responsible. The Fish and Wildlife Service is not even a member of the Coordinated Framework, where it might make most sense to make these decisions. In addition, no consistent and/or required risk assessment has been defined yet."

Where national level risk assessment is concerned, some respondents pointed to the National Environmental Policy Act (NEPA) assessment process as a potential model to extend. One interviewee commented, "It seems like the NEPA process is a good way to go through a process that is pretty complex to involve the public, get their input, involve the federal government, the state government, the local community, and everybody in the process to come to a decision. And that decision is recorded and documented so I think is a good way to go through the process."

However, gene drives implicate a diverse set of stakeholders and affected publics through their novel effects on the environment, potentially challenging classic modes of environmental assessment processes that have been used for previous conservation techniques. As indicated by one respondent, novel developments are needed to cope with genetic conservation technologies: "I think that this technology is very unique, and I don't know of too many cases where we have gone through the NEPA process for genetic reasons…[I]t is new ground, and I think that something more than just the current NEPA process is needed to be able to get the public to understand, to get them to care, to get them to have buy in. It will take a lot. I don't know what that is yet, but there will be lot of energy needed to get us there."

International Governance

> *"Potential release is about reflection and deliberation, being able to have, to be assured that any release is transparently governed, in ways that are democratic and open, where there is clear reversibility, that the experiment can be stopped at any moment and reversed, and that those who are negatively impacted have a say in it. On the scale of gene drives, it is going to be difficult to do this because it is transboundary."*

Respondents also discussed the importance of the 'transboundary nature of gene drives' and its implications for international governance. The risk of unintentional spread across national borders and other biosecurity concerns breeds a host of issues related to responsibility and accountability, with no clear indication of how such issues would be remedied given the complexity and variability that exists between the laws and regulations of different countries. Respondents mentioned a number of applicable frameworks and international governance mechanisms that might come into play:

- UN Convention on Biological Diversity to determine governance norms for gene drives.
- National Environmental Policy Act assessment process as a model to engage international entities in governance decisions around gene drives.
- World Health Organization framework for genetically modified mosquitoes to guide progression from laboratory research to field trials to release.

One respondent shared an example of a relevant project that is working through transboundary governance issues through the involvement of multiple national and international agencies: "I think it involves collecting opinions from every organization that is involved. So [we] present regularly…to make sure that the World Health Organization is informed and that they have technical input…We work with the regulatory agencies in the countries where we are doing the research. It depends where the agency actually sits. So there is the Ministry of Health but then the Ministry of the Environment is frequently involved. There is the National Biosafety Authority. And in some cases …the Ministry of Education is even involved."

Respondents communicated many different views about how governance should proceed, often emphasizing the priority of one scale of governance over another. For example, those in favor of a moratorium often prioritized the achievement of international governance, presumably a very challenging task, while those with more supportive views of the technology seemed to emphasize the importance of local governance or existing national regulatory structures.

Chapter 4: Conclusions and Recommendations

Chapter 4: Conclusions and Recommendations

Stakeholder interview feedback suggests the following key conclusions and recommendations for those funding and/or developing a gene drive mouse for biodiversity protection in an island context.

1. RISKS AND BENEFITS

1.1 Key perceived risks included actual efficacy of gene drives, off-target impacts, the ability to control gene drives, the unknowns, and broader implications for health, the environment, and society.

1.2 Key perceived benefits, in addition to the benefits of invasive rodent eradication for island biodiversity protection, focused on how gene drives differ from existing eradication methods (with attention to efficiency, efficacy, scalability, cost-effectiveness, and reduction of off-target effects).

1.3 Risk assessment should help to evaluate perceived benefits and risks **in comparison to other methodologies** and enable those engaging with communities and stakeholders to answer questions about risks, benefits, and uncertainties.

2. SCENARIOS FOR ISLAND SELECTION & GENE DRIVE DEVELOPMENT

2.1 For those supportive of field trials, a phased approach of beginning trials in simple environments, followed by more complex environments, was generally recommended. Stakeholders described benefits of enacting field trials in simple environments (where control is easier, traditional eradication could be deployed, and success is more likely) but also described the ultimate benefit of demonstrating the technology in complex environments (where the advantages of a gene drive strategy would be clear in comparison to existing technologies).

2.2 For those opposed to gene drives, there was no recommended safe nor appropriate scenario in which to begin field trials.

2.3 Stakeholders differed in their beliefs about impacts on public perceptions of whether a gene drive is transgenic or cisgenic. Many noted that **gene drives will be linked to broad public debates about GMOs regardless of the specifics of the technology.**

3. TRUST

3.1 No source of information was seen as categorically unbiased, with calls for transparency across sectors as a common precursor for trust. Themes of bias, conflict of interest, and transparency strongly influenced discussions of trust.

3.2 Because no for-profit entities are yet visible in gene drive research, critique focuses on other markers of bias, such as funding sources (e.g., the military), the "interests" of scientific teams in promoting their research and technology, and prior value commitments of NGOs and other political actors.

3.3 Stakeholders tended to trust formal, expert sources for information, such as university researchers and government agencies, while perceiving citizens as primarily trusting friends, family, and local community networks. Relatedly, they believed that citizens have different metrics for risks and benefits than experts. If accurate, these differences suggest that **engagement activities focused solely on communication by formal experts may not be sufficient for broader public engagement.**

4. ENGAGEMENT

4.1 Many stakeholders emphasized the **importance of involving local entities as trusted sources of information.** One strategy would be to engage local communities well before plans for field trials are finalized. Another strategy would be to recognize the need for a significant pause in field trial planning once a field trial site is identified, with time and resources allocated to significant engagement among scientists, community leaders, and conservation advocates. For uninhab-

ited islands, engagement of relevant stakeholders and communities remains important.

4.2 Stakeholders said **it was important not to be too "pushy" about the issue and agenda that are the focus of engagement, especially if those facilitating engagement come from outside the community.** Alignment between project goals and community values and priorities is critical.

4.3 It is important for community participants to feel that sharing their perspectives and opinions is influential as a "tool for actually determining an outcome" and that they are **not serving a role of simply "checking off a box for community engagement."** If engagement ultimately is inhibitory (i.e., the location is not chosen due to a community's lack of acceptance), this would be consistent with the purpose of engagement in enabling the community to help determine both whether and how a trial is conducted.

5. GOVERNANCE

5.1 Stakeholders communicated many different views about how governance should proceed, often emphasizing the priority of one scale of governance over another. **Any emphasis on one scale of governance over others is likely to foster criticism, which points to the importance of a strategy that attends to multiple scales of governance at each step.** For example, those in favor of a moratorium often prioritized the achievement of international governance (a very challenging task), while those with more supportive views of the technology seemed to emphasize the importance of local governance or existing national regulatory structures.

5.2 Stakeholders noted that **it may be necessary to incorporate national level agencies not previously involved in the governance of biotechnology.** One stakeholder commented, "For example, for control of a modified invasive species on an island, it is not clear to me which agency would be responsible. The Fish and Wildlife Service is not even a member of the Coordinated Framework, where it might make most sense to make these decisions."

5.3 Some stakeholders objected to the framing of our interviews as narrowly focused on gene drive rodents for conservation purposes, **mentioning greater concerns regarding their potential applications for agricultural and military purposes.** They emphasized seeing gene drives as a "platform technology" with huge implications. This presents a challenge to a process that emphasizes careful consideration of risks and benefits of a particular application of the technology (such as gene drive rodents for conservation).

5.4 Stakeholders differed in their view of the potential for adaptive management in the face of uncertainty. Some expressed a desire for reducing scientific, regulatory, social, and ecological uncertainty prior to field trials (and further laboratory research, in some cases). Others preferred a phased and cautious approach that would reveal potential problems in ways that could be managed as research moved toward broader deployment. At the extreme, one interviewee said, "it doesn't matter because...there is no safe way to experiment with these technologies in the wild." This reflects different value orientations as well as different levels of trust in decisions made about managing risks during research and field trials.

While these takeaways are drawn specifically from stakeholder interviews regarding a gene drive mouse for biodiversity protection on islands, many are likely to apply to other Safe Genes-funded projects in human health, food and agriculture, and defense. However, because interviews did not specifically explore perspectives on other applications, caution should be exercised in assuming transferability of takeaways.

For some stakeholders, significant concerns about gene drives as a platform technology will likely endure regardless of applications. For others, the perceived risks, benefits and tradeoffs of a gene

drive mouse for protecting island biodiversity may differ from those perceived for other gene drive applications—for example, a gene drive mosquito for reduction of malaria incidence in humans in mainland settings. Accordingly, a final recommendation of the engagement team that authored this report is that stakeholder and community engagement is an essential component of gene drive research in order to 1) create an understanding of the various perspectives associated with gene drives, in general, as well as with context-specific applications, and 2) ensure that these perspectives inform decisions regarding whether and how gene drives are developed and utilized.

Appendix: Stakeholder Interview Questions

'Demographic' Questions:

1. Please describe your current professional role.
2. How would you describe your professional training and experience, in a general sense (e.g., lawyer, conservation biologist, environmental advocate, regulator, etc.)
3. With which sector (or sectors, if multiple) do you most align? (options: academic/research; civil society/NGO; government/regulatory (specify: federal, state, local); private citizen; for-profit/business; other)
4. In what state do you reside (or, if not in the U.S., please specify country)?
5. Where/In what geographies do you work?

Basic Issue Framing Questions:

6. Please describe the work you have done/are currently doing (at all) related to biodiversity conservation, invasive rodent control, gene editing, and/or gene drives.
7. Please describe any work you have done in terms of public outreach, stakeholder engagement, or community consultation.
8. What are your personal thoughts and/or positions about gene editing and conservation?
9. Is there any difference between the personal interests you just described and those of your organization?

Risk vs. Benefit Questions about Gene Drives for Rodent Control:

10. In general, do you believe that control/eradication of invasive rodents on islands is an important conservation objective? (yes, no, not sure -- and please explain)
11. In your view, what are the most significant potential benefits of the use of gene drives to control invasive rodents on islands (if any)?
12. In your view, what are the most significant potential risks of the use of gene drives to control invasive rodents on islands (if any)?
13. How do gene drives compare to other rodent control technologies (e.g., traps, rodenticides) (better, worse, not certain – and why?)
14. How much does each of the following matter when considering risks and benefits, and why?
    a. Whether gene drives are being considered for inhabited vs. uninhabited islands
    b. The physical geography of the island in question
    c. The remoteness of the island in question
    d. Whether the gene drives are transgenic (e.g., genes from one species are used in a different species) or not

Stakeholder, Community Engagement, and Governance Questions:

15. Who do you most trust as a source of information on the risks and benefits of gene drives to control invasive rodents on islands? Whom do you not trust?
16. Thinking about citizens, more generally, who do you think they would trust most as a source of information about gene drive rodents? Whom would they not trust?

17. In your own experiences with stakeholder and community engagement on these topics, what have been your takeaways or lessons learned? For example: What issues commonly arise? What questions or discussions have been most important? What engagement approaches have worked best?

18. How should governance decisions regarding the following be made? What processes and criteria should be used, what information should they consider, and how should that information be incorporated (e.g., scientific data, public opinion, etc.)

a. research in the lab

b. field trials and release of invasive rodent gene drives on islands

Closing Questions:

19. Do you have any initial feedback/concerns about the project?

a. What should the scientists in the project pay attention to?

b. What should the funder of this stakeholder interview/engagement effort (DARPA) pay attention to?

20. What additional feedback would you like to provide on this topic at this time?

21. Who else would you recommend that we speak to on this subject (perhaps those who share your views and those who don't)?

a. Are there 'silent' or 'dormant' stakeholders that are not currently involved in this subject (perhaps at the research phase) but would have interests related to gene drives for invasive rodents (perhaps at the application phase)?