sustainability

MDPI

Perspective

Sustainability as a Framework for Considering Gene Drive Mice for Invasive Rodent Eradication

S. Kathleen Barnhill-Dilling *, Megan Serr, Dimitri V. Blondel and John Godwin

Department of Biological Sciences, College of Sciences, North Carolina State University, Raleigh, NC 27695, USA; meserr@ncsu.edu (M.S.); dvblonde@ncsu.edu (D.V.B.); godwin@ncsu.edu (J.G.)

* Correspondence: skbarnhi@ncsu.edu

Received: 30 January 2019; Accepted: 24 February 2019; Published: 4 March 2019

check for updates

Abstract: Gene drives represent a dynamic and controversial set of technologies with applications that range from mosquito control to the conservation of biological diversity on islands. Currently, gene drives are being developed in mice that may one day serve as an important tool for reducing invasive rodent pests, a key threat to island biodiversity and economies. Gene drives in mice are still in development in laboratories, and wild release of modified mice is likely a distant reality. However, technological changes outpace the existing capacity of regulatory frameworks, and thus require integrated governance frameworks. We suggest sustainability—which gives equal consideration to the environment, economy, and society—as one framework for addressing complexity and uncertainty in the governance of emerging gene drive technologies for invasive species management. We explore the impacts of rodent gene drives on island environments, including potential conservation and restoration of island biodiversity. We outline considerations for rodent gene drives on island economies, including impacts on agricultural and tourism losses, and reductions in biosecurity costs. Finally, we address the social dimension as an essential space for deliberation that will be integral to evaluating the potential deployment of gene drive rodents on islands.

Keywords: gene drives; invasive species management; sustainability

1. Introduction

Gene drive technologies have the capacity to alter shared environments significantly on multiple scales [1–4]. A dynamic and controversial set of technologies, applications range from mosquito control for malaria reduction to rodent control for the conservation of biological diversity on islands [5]. Currently, gene drives are being developed in house mice that may one day serve as an important tool in the reduction of invasive rodent pests, a key threat to island biodiversity and economic sustainability. Wild release of modified rodents is likely a distant reality. However, technological changes can unfold quickly and far outpace the existing capacity of regulatory frameworks. This absence of clear regulatory mechanisms creates the need for governance frameworks that integrate complexity and uncertainty. In fact, both biological and social scientists encourage transparent governance—where decisions are the result of broad and deliberative processes—and "responsible stewardship" around gene drive technologies before they are developed successfully in the lab [1,6].

The governance of gene drive technologies in particular has garnered significant national and international attention for the far-reaching implications, and for the absence of meaningful regulatory frameworks to govern gene drive organisms in the environment [5,7]. As such, alternative or supplementary governance processes have been put forth as a way to bridge the gap, and attend specifically to socio-cultural values that underpin different perspectives. This paper responds to the pressing need to identify interdisciplinary and flexible frameworks for the governance of gene drive technologies, particularly those that will be used for the eradication of invasive rodents. We suggest that the framework of sustainability is an important tool for governance of gene drive organisms, especially in the face of the uncertainty and complexity that characterize their applications more generally. That sustainability offers relatively equal weight to environmental, economic, and social dimensions is one of its strengths as a framework, particularly with respect to understanding the complex values and perceived risks that are entangled with these overlapping issues. Moreover, sustainability offers locally-placed but globally situated metrics for understanding the implications of gene drive technologies, where locally situated decisions are nested within global institutions and ecosystems [2].

2. Background

2.1. Invasive Rodents on Islands

Invasive rodents occur on over eighty percent of the world's islands [8]. The four species of primary concern are house mice (*Mus musculus*) and three species of rats (*Rattus rattus*, *R. norvegicus*, *R. exulans*) [9]. Rodents invade easily with human transportation, and are able to rapidly establish populations and adapt to island environments. As a result, house mice are the second most widespread mammal on the planet after humans [10,11].

Negative impacts of invasive rodents are widespread, and islands are particularly vulnerable to their effects [12]. For example, as disease vectors, invasive rodents represent a public health hazard. Invasive rodents are also responsible for considerable biodiversity losses on islands [13,14]. Islands are often home to endemic species, or species found nowhere else on Earth, and these native species have often evolved without predators [15]. As a result, island species are often particularly vulnerable to invasive species. Moreover, island economies are often less resilient and more vulnerable to external pressures, due to their relatively limited size and heavy reliance on natural resources, and invasive rodents also negatively impact agricultural and tourism economies on islands [16]. Additionally, because they are often direct vectors of infectious diseases, invasive rodents can present public health concerns [14].

Because of their ubiquity and deleterious impacts, numerous eradication efforts have been undertaken to rid islands of invasive rats and mice [8,15]. These eradication efforts have been successful in eliminating invasive rodents from over 400 islands [17]. However, eradications rely almost exclusively on rodenticides which present a number of challenges, including high failure rates, off-target effects that can negatively impact conservation species of concern, and high operational costs [13,14,18]. Moreover, rodenticide-based eradications are only effective—or even possible—on approximately 15% of affected islands [15]. These and other challenges have created a compelling need for alternative approaches to rodent eradication.

2.2. Gene Drives as Possible Solution

Synthetic gene drive technologies represent one promising but controversial potential alternative solution to rodenticide-based eradication approaches. Gene drives are systems of inheritance that move a particular trait into a population even if the gene drive produces a fitness cost to the organism [19]. Unlike the traditional Mendelian ratio of a 50% chance for inheritance, gene drives can potentially transmit a trait to offspring at near 100% ratios. By themselves, gene drives are not inherently new concepts: There are a number of naturally occurring 'selfish' genetic traits that serve as gene drives in wild populations [19]. In fact, the development of gene drive mice relies heavily on naturally occurring gene drive functions [5,6] However, the advent of new and powerful genome editing capabilities enabled by CRISPR technologies has accelerated the development of synthetic gene drives and potential environmental release of genome-edited organisms [1]. Synthetic gene drives have thus far been successfully developed in mosquitoes, flies, worms, and yeast [1,19–23].

Sex biasing gene drives—whereby a trait that drives the population to mostly male or mostly female—is being considered for invasive species eradication [1,23,24]. Modeling suggests that these gene drives could be engineered to spread to all members of a population from a release of a few individuals [25,26]. Sex biasing gene drives are being developed in mice as both target species and as model species. Biasing the sex ratio of a particular population would cause local extirpation, due to a lack of suitable mates [6,14]. As such, gene drives could be used to reduce invasive rodent populations on islands. A comparison of rodenticide and potential gene drive eradications can be found in Table 1.

Table 1. Potential eradication methods: A comparison.

	Rodenticides	**Gene Drives**
Function	Brodifacoum:Second generation anticoagulants—lethal upon ingestion	Using CRISPR mice to ensure all mice look and behave male or female
Efficacy	At least to 38% failure rate for house mice; 5–10% failure rates for rats	Unknown—modeling predicts high success with minimum release rate
Monetary Cost	Millions of dollars per island; fixed costs	High upfront costs; predicted to diminish over time
Pros	• Established protocol • Higher success rate for rats (*Rattus*) • Clear regulatory frameworks in place	• Species-specific • Safe to use around humans, pets and livestock • Non-lethal method • Absence of regulatory frameworks
Cons	• Inhumane • Non-target effects • Difficult to employ on human-inhabited islands • High fixed costs	• Potentially controversial • Biosecurity protocols still being developed
Biosecurity	• Contained geographically • Toxicant degrades over time • Only security concern is re-introduction of invasive rodent	• Requires a minimum release threshold • Genetic/molecular methods of containment in progress

Adapted from Leitschuh et al., 2018 [14].

Gene drives may offer a number of environmental and economic benefits to the management of invasive rodents on islands. However, they also emerge in complex human systems. In fact, despite considerable technological and ecological uncertainty one of the most significant potential barriers to the use of gene drive rodents is the potential for socio-political opposition about the environmental release of gene drive rodents [7]. As such, the issue of gene drive rodents for island invasive species management calls for a framework that can give equal attention to environmental, economic, and social considerations.

3. Sustainability

This paper explores how the three pillars of sustainability—environment, economy, and society—can serve as an important framework for governing gene drive rodents for island conservation. Sustainability is certainly a broadly used term, and until operationalized in a particular context, can have a variety of implications. Significant sustainability scholarship attends to the extended lifetime of a particular resource system [27] which while important to consider more broadly, offers a distinct perspective on environmental governance. We employ the framework of sustainability that, in decision-making, attends equally to environmental, social, and economic considerations [28].

Larson and colleagues already call for sustainability as a framework for invasive species management, in part because invasive species management decisions are often made without giving social and economic factors sufficient consideration [16]. We argue that a sustainability framework is particularly important for invasive species management and rodent eradication schemes that include gene drive organisms, because a significant drawback to potentially using gene drive rodents for invasive species management is potential socio-political opposition [29].

We engage with each of the three dimensions of sustainability in turn—environment, economy, and society—to demonstrate how this framework can help shape responsible and just governance of mammalian gene drives. We explore the impacts of rodent gene drives on island *environments*, including potential conservation and restoration of island biodiversity, improved animal welfare, and a reduction in off-target effects. We evaluate rodent gene drives on island *economies*, interrogating anticipated reductions in agricultural and tourism losses, biosecurity costs, and offsetting costly rodenticide applications. Finally, the *society* pillar creates essential space for deliberation, and important dimensions of governance that will be integral to evaluating the potential deployment of gene drive rodents on islands. Each of these three pillars encapsulates textured and complex debate and as such, this paper provides a broad overview of these dimensions.

3.1. Environment

Islands represent approximately five percent of the world's terrestrial land mass, but thirty-seven percent of all critically endangered species are endemic to islands [30]. Endemic island species, species that are found only on particular islands, are especially vulnerable to invasive species, because they evolved in relative isolation and may lack defenses against predators from the mainland [15]. Conserving and restoring island biodiversity by reducing or eliminating invasive species, according to many stakeholders, represents an important and inherently positive endeavor.

Invasive rodents can be particularly damaging to island ecosystems, and an estimated 80% of the world's islands harbor invasive rodents [9,31]. Rodents are direct viral and bacterial disease vectors for humans and other animals, and are reservoirs for dozens of infection pathogens [14]. Invasive rodents can also severely impact ecosystems, especially on islands where native biota evolved in the absence of mammalian predators [32–34]. For example, islands are often the nesting and breeding grounds for seabirds. Rodents can have devastating impacts on seabird populations by consuming eggs and harming chicks [9,35]. In fact, "invasive rodents have been implicated in the extinction of over 60 vertebrates alone" [14] (pp. 5121–5122). In short, invasive rodents are a significant biodiversity threat for the majority of the world's islands.

Introduced predators can also have significant indirect but large-scale impacts on entire island ecosystems [26,35]. The impacts of species restoration are intended to have broader restorative effects throughout island ecosystems [36–38]. For example, scientists have demonstrated that removing invasive rodents benefits native flora and fauna, particularly by increasing seabird fecundity [38,39]. Following rat eradication on Palmyra Atoll, the non-native Asian tiger mosquito (*Aedes albopictus*)—which was a known infectious disease vector–underwent a secondary local extirpation [40]. Additionally, recent scholarship suggests that coral reefs can benefit from the eradication of invasive rodents as seabirds enhance the productivity of coral reefs [37].

Current efforts to eradicate invasive rodents also present animal welfare concerns. As noted above, currently the primary means of removing invasive rodents from islands greater than five hectares is rodenticides [13]. As of 2015, over 650 rodenticide-based eradication campaigns have been launched worldwide [41]. Rodenticides are anticoagulants that are lethal when ingested [39], and are not species-specific, resulting in accidental consumption by the species that efforts aim to protect [13,18,42]. For aerial campaigns, native species must often be captured and contained to prevent death by accidental ingestion. On human-inhabited islands, eradication is particularly challenging, because of the potential for accidental human or livestock consumption [13,42]. Moreover, complete eradication is not always feasible requiring repeated efforts, and resistance to rodenticides can emerge [8,10]. By comparison, released gene drive rodent control may result in short-term increases of local rodent populations, but once established, should drive down populations by preventing births, as opposed to causing painful deaths [14,19].

Many proponents consider gene drive biocontrol to have clear comparative advantages over other eradication methods [6,13]. Current rodenticide-based eradication methods can only effectively eliminate rodent populations on 15% of impacted islands, and effectively preserving island biodiversity calls for transformative methods, such as the application of gene drives for genetic rodent control [13]. Additionally, ongoing ecological and population dynamic modeling can aid the further understand of how gene drives may behave in the environment [25,43], and support decision-making in the face of considerable uncertainty. There is still considerable precaution, or even opposition, to using gene drive mice for any purposes, particularly species conservation [5]. Invasive species eradication, however, still calls for complex matrices and bases for decision-making, particularly those that address economic and social considerations.

3.2. Economy

From an economic perspective, invasive rodents can present problems for island agriculture and economically vital island tourism industries [44]. Islands often have small economies, their relative size rendering them less resilient and therefore more vulnerable to external pressures, such as those caused by invasive rodent species [16], and this vulnerability is an important consideration. The impacts of removing invasive rodents through gene drives are predicted to improve agricultural economies and tourism economies while potentially reducing costs of eradication efforts overall.

The most direct economic impact of invasive rodents is on agriculture [45]. Rodents are responsible for large crop losses (14–66%) to important crops, including maize, soybean and rice [34]. Significant damage can occur at any stage of crop development, from rodents digging up freshly planted seeds to damaging stored and transported goods [46]. In Australia, house mouse outbreaks occur every few years and often reach plague proportions of >800 mice ha^{-1} [47]. These outbreaks disrupt farmers' livelihoods and considerable efforts have been undertaken to predict and manage outbreaks [47]. Where mice cause agricultural damage, the ability to relate mouse density to crop damage can allow for proper calculations of economic injury levels and allow for the formation of damage thresholds [46]. Damage threshold calculations could help calculate the number of mice present before management options should be employed [46].

The rodenticides that are used for eradication are second-generation anticoagulants that are lethal when ingested [29]. Rodenticide application programs are complex operations; their planning and implementation include challenges, such as multi-phased personnel costs and transportation to remote islands [14]. When these plans are implemented, rodenticides are broadcast from helicopters, and through the deployment of bait stations, bait trays, and even manually [29]. The high fixed cost of these toxicant-based rodent eradication is one of the factors limiting their current use and effectiveness [13,14]. These costs can reach millions of dollars per island [13,48]; in 2012 more than US$600 million were spent globally on rodenticides, with projections of up to US$900 million by 2019 [13,49]. While mouse gene drives have been estimated to cost millions of dollars to develop, these anticipated costs are estimated to be considerably lower than what is currently being spent on rodenticide-based rodent eradication programs [14], particularly when accounting for potential costs accrued from non-target effects [48].

Tourism economies are also impacted by rodent eradication. There are long-term tourism costs to ignoring eradication, including a decline in values and tourism experience in areas expected to be natural, "unspoilt" parts of the world [29], providing additional motivation for rodent eradication. Based on cost-benefit analyses and willingness to pay calculations, tourism-related revenues are expected to increase post-eradication [29,50]. Rodenticide eradication programs that include helicopter broadcasts and manual baiting also result in projected short-term tourism losses; tourists may not visiting during the eradication program [29]. Gene drive biocontrol could still result in the same long-term tourism benefits as rodenticide-based control, but using gene drive mice as an alternative will likely reduce the impacts of these tourism gaps, since they involve the release of mice and subsequent sampling rather than broadly distributed toxicants.

Additional economic factors to consider include biosecurity and biosafety safeguards. Biosecurity concerns center around getting and keeping invasive rodents off islands. Some of the associated biosecurity costs—primarily those associated with reinvasion–are seen as relatively consistent across the different eradication methods. For example, despite the strength of an ocean barrier, human-mediated introductions (and reintroductions) are considered a high risk [51] and these introductions often occur in tandem with tourism traffic via equipment and vessels [52]. Island borders and ports must thus either be regulated [52] or in the cases of unmonitored public access borders, islands must be extensively monitored and managed in other ways [51]. While recent technological advances, such as biomarker tools and molecular tools have proven quite effective [51–54], they still represent a cost to rodent re-invasion prevention.

The use of gene drive biocontrol could reduce some costs associated with rodenticide eradications, including eliminating the often costly need for non-target species management, since a gene drive would be species-specific unlike rodenticides. However, this would depend on the approach used. For example, in the '*t*-Sry' system a naturally occurring gene drive termed the *t*-haplotype would be modified by the addition of the key male determining gene *Sry* to masculinize offspring sex ratios (see References [6,14] for fuller descriptions]. However, mathematical modeling suggests this particular approach would likely require multiple releases of gene drive animals to achieve eradication [25]. Multiple releases would be part of the broader strategy to reduce the likelihood of uncontrolled spread [55]. Another potential cost benefit for gene drive approaches could be realized by eliminating the concerns described above regarding the use of rodenticide approaches on inhabited islands. Because the gene drive mice are still in the laboratory development phase, one must also consider the relative risk of sinking resources into a high stakes project that may not successfully produce gene drive mice that work as hoped or designed [56].

Biosafety concerns, on the other hand, center around keeping an organism within the geographic space for which it is intended [57]. Biosafety concerns are distinct from current eradication plans, because unlike rodenticides, some gene drive designs have the ability to self-propagate [1,14], and even escape from the island for which it is designed. For this reason, the drive should be designed carefully to prevent effects on nearby mainland mice. Researchers are currently developing such built-in geographic and temporal safeguards [14]. "Locally fixed alleles" represents one gene drive biosafety strategy, that targets certain alleles which are specific to a given island. If gene drive animals with locally fixed alleles were to escape, they should have no effect on mainland populations [43]. Because this strategy is embedded in the development of the gene drive mice, it does not represent an additional biosafety cost.

Although economic analyses of gene drive applications for invasive species eradication are still in early stages [13]. Economic losses from invasive species, and the potentially reduced costs of eradication programs using gene drive mice, offer some foundation for these analyses. A cost-benefit analysis that compares the cost of rodenticide eradication and integrates projected costs of technology development and phased release represents an important need in the scholarship surrounding gene drive-based invasive species management.

3.3. Society

Social considerations for gene drive rodents represent perhaps the most complex dimension of the sustainability framework, and may well be the deciding factor in the application of gene drives more broadly [29]. The possible release of gene drive rodents as an invasive species eradication strategy is situated at the intersection of two already complex and controversial domains: Gene drives and invasive species management. In fact, the social dimensions that underpin invasive species management and emerging gene drive biotechnologies share important characteristics. Perceptions of invasive species management and gene drive technologies both draw on diverse social perspectives, value systems, and risk perceptions that are built on psychological, cultural, or even evolutionary factors [16,58]. Both issues also require space to integrate highly technical or scientific information, heavily values-laden perspectives, and decision-making in the face of considerable uncertainty [5]. As such, a governance approach is called for [2,59] that attends to the complexity of both invasive species management and gene drives, both of which engage with disparate values and different perceptions of risk.

The development of these technologies is outpacing the local, national and global structures that govern biotechnology in the environment [2], and some scholars describe them as 'anomalies' in the biotechnology regulation ecosystem [60]. Gene drive organisms will not only cross political jurisdictions, but they will also influence shared environments and decisions about them should reflect these complex implications [2,59]. As such, attention turns to the *governance* of these technologies. Governance—distinct from governments—is a rightfully broad concept that draws on a variety of actors and institutions that would broaden the scope of responsibility of oversight from mandatory government regulations to also include voluntary standards or norms that address scientific ethics and respect for impacted communities [5]. An important feature of governance is the potential for deliberative engagement with communities, stakeholders, and public audiences about the technological innovation, their potential hazards and benefits, and the values that underpin these different positions [7,58,59].

One governance approach that can attend to complex values and risk perceptions—and is consistent with calls in the governance of emerging gene editing or biotechnologies—is a deliberative community, stakeholder, and public engagement [5]. This concept represents a gradient of groups: Communities are generally considered to be characterized by geographic proximity to project impact, while stakeholders have some professional or personal interest [5]. Public audiences or groups may not be characterized by the same geographic or professional connection, but they are comprised of individuals who have some interest or concerns. That gene drive mice for conservation are designed to impact shared environments makes all three of these categories important [5]. Additionally, we use the definition of engagement from the gene drive report from the National Academies of Sciences, Engineering, and Medicine: "[S]eeking and facilitating the sharing and exchange of knowledge, perspectives, and preferences between or among groups who often have differences in expertise, power, and values" [5] (pp. 132). The focus on deliberation in this context is clear. Deliberative engagement processes also have the potential to generate decision outcomes that can balance competing priorities of different perspectives. Appropriately timed community, stakeholder, and public engagement situated within the framework of sustainability can facilitate decision spaces that attend to the range of social, economic, and environmental concerns that are associated with gene drive rodents for invasive species management.

Standpoints about using gene drive rodents as invasive species management tools are inevitably values-based. Values are deeply held beliefs that are broadly tied to individual and group identity [58]. One important set of values-focused questions related to this particular case are perspectives about the human relationship to the natural environment, including conceptualizations of what is considered natural (or by opposed, unnatural). The use of a gene drive organism represents a problematic departure from what some values systems consider to be natural, whereas other groups may see the use of these technologies as a means of restoring ecosystems to a more natural state. In fact, some groups may see the gene drive organisms to be a significantly greater threat to island environments than the invasive rodents themselves [4]. A second set of values to consider is perspectives about fairness or justice: In particular, who benefits from these technologies, and who gets to make decisions about them? Community, stakeholder, and public engagement offer potential for engaging in inclusive deliberative processes that holds space for competing values.

Relatedly, values underpin disparate risk perceptions about the potential use of gene drive mice for invasive species eradication. Here we consider risk from the colloquial perspective, as well as the probabilistic perspective, where likelihoods of benefits and hazards are quantified [61]. Emerging biotechnologies are often framed in terms of potential risk, yet the regulatory frameworks that govern risk attend explicitly to verifiable scientific risk that masks underlying value judgements [61].

For example, risk is quantified through the calculation of likely endpoints; these endpoints are identified as either harms, hazards, or benefits. The framing and identification of each endpoint as either harm, hazard, or benefit, for example, are inherently value judgements. Community, stakeholder, and public engagement processes offer the potential to deliberate about these endpoints, a particularly important idea to engage broadly since gene drive technologies may fundamentally reshape local social-ecological systems across spatial and temporal scales.

Moreover, while some scholars have warned against a possible "risk panic" with respect to gene drives, others have noted the equally problematic potential for "innovation thrill," where the promise of a technology clouds careful and deliberative decision-making [62]. Ideally, engagement could temper either end of the spectrum, creating space for meaningful dialogue about the potential use of gene drive organisms. Community, stakeholder, and public engagement will play a vital role in the governance of gene drive rodents for invasive species management and eradication.

4. Discussion

In short, decisions about the use of gene drive organisms for any application will require thoughtful and inclusive deliberation [60]. The promise of these technologies is great, yet the uncertainty about success outcomes is clearly considerable. Importantly, scholars and innovators alike are drawing attention to questions about who gets to make decisions about gene drive uses, and to questions about the bases on which these decisions will be made [7,55,59]. We argue that sustainability offers one interdisciplinary and flexible framework for anchoring broad governance questions around the use of gene drive technologies, providing some guidance for complex decisions.

Here, we have identified how the three pillars of environment, economy, and society can be used to consider gene drive rodents for the conservation of island biodiversity. The underlying motivation for these gene drive applications is inherently an environmental issue, and the case for gene drives as boosting island economies can be made. Yet, the value of the sustainability framework lies in how it attends equally to social considerations: Here we see that unpacking the values embedded in these issues complicates the assumptions that underpin environmental and economic benefits. Island communities are inherently vulnerable to global environmental change [12,44], and tools for sustainability and resilience should be explored carefully.

Islands also offer important insight into the balance of making decisions in local communities that are situated in systems of global governance. Gene drive organisms are being addressed in a variety of international fora, such as the Convention on Biological Diversity and the International Union for the Conservation of Nature [2]. These are important scales of governance for environmental release of gene drive organisms with global consequences. However, the most direct effects of gene drive organisms will, in fact, be on local communities and as such, local community governance should be central to related decisions. Islands are by nature both relatively isolated and networked to global systems; the arrival and threat of invasive rodents reflect this context. Importantly, this is the nature and scale of governance that Kofler and collaborators call for: Locally situated governance with global vision [2]. As such, an examination of gene drive mice as a tool for invasive rodent eradication is important for both the immediate case, but also for other applications of gene drive organisms. Here, the mouse is both a target and a model on multiple levels: Invasive mice are a target for eradication and a model species for mammalian gene drives more generally. The governance of gene drive mice has similar parallels: The potential use of gene drive mice will have important implications for island biodiversity conservation in its own right, and the decisions and impacts made will also be instructive for other applications and systems. As such, gene drive mice offers opportunity as both genetic model system, as well as a social science model system. Using sustainability as a guiding framework offers important insight for making decisions that may have global implications.

Author Contributions: Conceptualization, S.K.B.-D.; Writing—Original Draft Preparation, S.K.B.-D; M.S. & D.V.B.; Writing—Review & Editing, S.K.B.-D. & J.G.; Supervision, J.G.; Project Administration, S.K.B.-D; Funding Acquisition, J.G.

Funding: John Godwin receives support from the Defense Advanced Research Projects Agency Safe Genes program (SAFE-FP-005).

Conflicts of Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. All authors participate in the Genetic Biocontrol of Invasive Rodents partnership (www.geneticbiocontrol.org).

References

1. Esvelt, K.M.; Smidler, A.L.; Catteruccia, F.; Church, G.M. Emerging technology: Concerning RNA-guided gene drives for the alteration of wild populations. *eLife* **2014**, *3*, e03401. [CrossRef] [PubMed]
2. Kofler, N.; Collins, J.P.; Kuzma, J.; Marris, E.; Esvelt, K.; Nelson, M.P.; Newhouse, A.; Rothschild, J.L.; Vigliotti, V.S.; Semenov, M.; et al. Editing nature: Local roots of global governance. *Science* **2018**, *362*, 527–529. [CrossRef] [PubMed]
3. Ricciardi, A.; Blackburn, T.M.; Carlton, J.T.; Dick, J.T.; Hulme, P.E.; Iacarella, J.C.; Pyšek, P. Invasion science: A horizon scan of emerging challenges and opportunities. *Trends Ecol. Evol.* **2017**, *32*, 464–474. [CrossRef] [PubMed]
4. Webber, B.L.; Raghu, S.; Edwards, O.R. Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 10565–10567. [CrossRef] [PubMed]
5. National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*; National Academies Press: Washington, DC, USA, 2016.
6. Piaggio, A.J.; Segelbacher, G.; Seddon, P.J.; Alphey, L.; Bennett, E.L.; Carlson, R.H.; Friedman, R.M.; Kanavy, D.; Phelan, R. Is it time for synthetic biodiversity conservation? *Trends Ecol. Evol.* **2017**, *32*, 97–107. [CrossRef] [PubMed]
7. Kuzma, J.; Gould, F.; Brown, Z.; Collins, J.; Delborne, J.; Frow, E.; Esvelt, K.; Guston, D.; Leitschuh, C.; Oye, K.; et al. A roadmap for gene drives: Using institutional analysis and development to frame research needs and governance in a systems context. *J. Responsible Innov.* **2018**, *5* (Suppl. 1), S13–S39. [CrossRef]
8. Howald, G.; Donlan, C.J.; Galvan, J.P.; Russell, J.C.; Parkes, J.; Samaniego, A.; Wang, Y.; Veitch, D.; Genovesi, P.; Pascal, M.; et al. Invasive rodent eradication on islands. *Conserv. Biol.* **2007**, *21*, 1258–1268. [CrossRef] [PubMed]
9. Caut, S.; Angulo, E.; Courchamp, F. Dietary Shift of an Invasive Predator: Rats, Seabirds and Sea Turtles. *Source: J. Appl. Ecol.* **2008**, *45*, 428–437. [CrossRef] [PubMed]
10. Angel, A.; Wanless, R.M.; Cooper, J. Review of impacts of the introduced house mouse on islands in the Southern Ocean: Are mice equivalent to rats? *Biol. Invasions* **2009**, *11*, 1743–1754. [CrossRef]
11. MacKay, J.W.B.; Russell, J.C.; Murphy, E.C. Eradicating House Mice from Islands: Successes, Failures, and the Way Forward. In *Managing Vertebrate Invasive Species: Proceedings of an International Symposium*; Witmer, G.W., Pitt, W.C., Fagerstone, K.A., Eds.; USDA/APHIS Wildlife Services, National Wildlife Research Center: Fort Collins, CO, USA, 2007; pp. 293–304.
12. Russell, J.C.; Meyer, J.Y.; Holmes, N.D.; Pagad, S. Invasive alien species on islands: Impacts, distribution, interactions and management. *Environ. Conserv.* **2017**, *44*, 359–370. [CrossRef]
13. Campbell, K.J.; Beek, J.; Eason, C.T.; Glen, A.S.; Godwin, J.; Gould, F.; Holmes, N.D.; Howald, G.R.; Madden, F.M.; Ponder, J.B.; et al. The next generation of rodent eradications: Innovative technologies and tools to improve species specificity and increase their feasibility on islands. *Biol. Conserv.* **2015**, *185*, 47–58. [CrossRef]
14. Leitschuh, C.M.; Kanavy, D.; Backus, G.A.; Valdez, R.X.; Serr, M.; Pitts, E.A.; Threadgill, D.; Godwin, J. Developing gene drive technologies to eradicate invasive rodents from islands. *J. Responsible Innov.* **2018**, *5* (Suppl. 1), S121–S138. [CrossRef]
15. Bellard, C.; Cassey, P.; Blackburn, T.M. Alien species as a driver of recent extinctions. *Biol. Lett.* **2016**, *12*. [CrossRef] [PubMed]
16. Larson, D.L.; Phillips-Mao, L.; Quiram, G.; Sharpe, L.; Stark, R.; Sugita, S.; Weiler, A. A framework for sustainable invasive species management: Environmental, social, and economic objectives. *J. Environ. Manag.* **2011**, *92*, 14–22. [CrossRef] [PubMed]

17. Database of Island Invasive Species Eradications, developed by Island Conservation, Coastal Conservation Action Laboratory UCSC, IUCN SSC Invasive Species Specialist Group, University of Auckland and Landcare Research New Zealand. 2017. Available online: http://diise.islandconservation.org (accessed on 28 February 2019).
18. Rueda, D.; Campbell, K.J.; Fisher, P.; Cunninghame, F.; Ponder, J.B. Biologically significant residual persistence of brodifacoum in reptiles following invasive rodent eradication, Galapagos Islands, Ecuador. *Conserv. Evid.* **2016**, *13*, 38.
19. Champer, J.; Buchman, A.; Akbari, O.S. Cheating evolution: Engineering gene drives to manipulate the fate of wild populations. *Nature Rev. Genet.* **2016**, *17*, 146–159. Available online: https://www.nature.com/articles/nrg.2015.34 (accessed on 28 February 2019). [CrossRef] [PubMed]
20. DiCarlo, J.E.; Chavez, A.; Dietz, S.L.; Esvelt, K.M.; Church, G.M. Safeguarding CRISPR-Cas9 gene drives in yeast. *Nat. Biotechnol.* **2015**, *33*, 1250–1255. [CrossRef] [PubMed]
21. Gantz, V.M.; Bier, E. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science* **2015**, *6233*, 442–444. [CrossRef] [PubMed]
22. Harris, A.F.; Nimmo, D.; McKemey, A.R.; Kelly, N.; Scaife, S.; Donnelly, C.A.; Beech, C.; Petrie, W.D.; Alphey, L. Field performance of engineered male mosquitoes. *Nat. Biotechnol.* **2011**, *29*, 1034–1037. [CrossRef] [PubMed]
23. Sinkins, S.P.; Gould, F. Gene drive systems for insect disease vectors. *Nat. Rev. Genet.* **2006**, *7*, 427–435. [CrossRef] [PubMed]
24. Burt, A. Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proc. R. Soc. Lond. B Biol. Sci.* **2003**, *270*, 921–928. [CrossRef] [PubMed]
25. Backus, G.A.; Gross, K. Genetic engineering to eradicate invasive mice on islands: Modeling the efficiency and ecological impacts. *Ecosphere* **2016**, *7*. [CrossRef]
26. Prowse, T.A.; Cassey, P.; Ross, J.V.; Pfitzner, C.; Wittmann, T.A.; Thomas, P. Dodging silver bullets: Good CRISPR gene-drive design is critical for eradicating exotic vertebrates. *Proc. R. Soc. B* **2017**, *284*. [CrossRef] [PubMed]
27. Ostrom, E. A general framework for analyzing sustainability of social-ecological systems. *Science* **2009**, *325*, 419–422. [CrossRef] [PubMed]
28. Pope, J.; Annandale, D.; Morrison-Saunders, A. Conceptualising sustainability assessment. *Environ. Impact Assess. Rev.* **2004**, *24*, 595–616. [CrossRef]
29. Gillespie, R.; Bennett, J. Costs and benefits of rodent eradication on Lord Howe Island, Australia. *Ecol. Econ.* **2017**, *140*, 215–224. [CrossRef]
30. Tershy, B.R.; Shen, K.W.; Newton, K.M.; Holmes, N.D.; Croll, D.A. The importance of islands for the protection of biological and linguistic diversity. *Bioscience* **2015**, *65*, 592–597. [CrossRef]
31. Towns, D.R.; Atkinson, I.A.E.; Daugherty, C.H. Have the Harmful Effects of Introduced Rats on Islands been Exaggerated? *Biol. Invasions* **2006**, *8*, 863–891. [CrossRef]
32. Drake, D.R.; Hunt, T.L. Invasive rodents on islands: Integrating historical and contemporary ecology. *Biol. Invasions* **2009**, *11*, 1483–1487. [CrossRef]
33. Mulder, C.P.; Grant-Hoffman, M.N.; Towns, D.R.; Bellingham, P.J.; Wardle, D.A.; Durrett, M.S.; Fukami, T.; Bonner, K.I. Direct and indirect effects of rats: Does rat eradication restore ecosystem functioning of New Zealand seabird islands? *Biol. Invasions* **2009**, *11*, 1671–1688. [CrossRef]
34. Singleton, G.; Krebs, C. The Secret World of Wild Mice. In *The Mouse in Biomedical Research: History, Wild Mice, and Genetics*; Fox, J., Barthold, S., Davisson, C., Quimby, F., Smith, A., Eds.; Elsevier: Amsterdam, The Netherlands, 2007; pp. 25–51.
35. Fukami, T.; Wardle, D.A.; Bellingham, P.J.; Mulder, C.P.H.; Towns, D.R.; Yeates, G.W.; Bonner, K.I.; Durrett, M.S.; Grant-Hoffman, M.N.; Williamson, W.M. Above- and below-ground impacts of introduced predators in seabird-dominated island ecosystems. *Ecol. Lett.* **2006**, *9*, 1299–1307. [CrossRef] [PubMed]
36. Croll, D.A.; Maron, J.L.; Estes, J.A.; Danner, E.M.; Byrd, G.V. Introduced predators transform subarctic islands from grasslands to tundra. *Science* **2005**, *307*, 1959–1961. [CrossRef] [PubMed]
37. Graham, N.A.J.; Wilson, S.K.; Carr, P.; Hoey, A.S.; Jennings, S.; Macneil, M.A. Seabirds enhance coral reef productivity and functioning in the absence of invasive rats. *Nature* **2018**, *559*, 250–253. [CrossRef] [PubMed]

38. Jones, H.P.; Holmes, N.D.; Butchart, S.H.; Tershy, B.R.; Kappes, P.J.; Corkery, I.; Aguirre-Muñoz, A.; Armstrong, D.P.; Bonnaud, E.; Burbidge, A.A.; et al. Invasive mammal eradication on islands results in substantial conservation gains. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 4033–4038. [CrossRef] [PubMed]
39. Capizzi, D.; Bertolino, S.; Mortelliti, A. Rating the rat: Global patterns and research priorities in impacts and management of rodent pests. *Mammal Rev.* **2014**, *44*, 148–162. [CrossRef]
40. Lafferty, K.D.; McLaughlin, J.P.; Gruner, D.S.; Bogar, T.A.; Bui, A.; Childress, J.N.; Espinoza, M.; Forbes, E.S.; Johnston, C.A.; Klope, M.; et al. Local extinction of the Asian tiger mosquito (Aedes albopictus) following rat eradication on Palmyra Atoll. *Biol. Lett.* **2018**, *14*. [CrossRef] [PubMed]
41. Russell, J.C.; Holmes, N.D. Tropical island conservation: Rat eradication for species recovery. *Biol. Conserv.* **2015**, *185*, 1–7. [CrossRef]
42. Parkes, J.; Fisher, P.; Forrester, G. Diagnosing the cause of failure to eradicate introduced rodents on islands: Brodifacoum versus diphacinone and method of bait delivery. *Conserv. Evid.* **2011**, *8*, 100–106.
43. Sudweeks, J.; Hollingsworth, B.; Blondel, D.V.; Campbell, K.J.; Dhole, S.; Eisemann, J.D.; Edwards, O.; Godwin, J.; Howald, G.R.; Oh, K. Locally Fixed Alleles: A method to localize gene drive to island populations. *bioRxiv* **2019**, 509364. [CrossRef]
44. Reaser, J.K.; Meyerson, L.A.; Cronk, Q.; De Poorter, M.A.J.; Eldrege, L.G.; Green, E.; Kairo, M.; Latasi, P.; Mack, R.N.; Mauremootoo, J.; et al. Ecological and socioeconomic impacts of invasive alien species in island ecosystems. *Environ. Conserv.* **2007**, *34*, 98–111. [CrossRef]
45. Brown, P.R.; Singleton, G. Impacts of House Mice on Crops in Australia–Costs and Damage. Natural Resources Management and Policy Commons: Human Conflicts with Wildlife: Economic Considerations. 2000. Available online: https://digitalcommons.unl.edu/nwrchumanconflicts/6/ (accessed on 28 February 2019).
46. Brown, P.R.; Huth, N.I.; Banks, P.B.; Singleton, G.R. Relationship between abundance of rodents and damage to agricultural crops. *Agric. Ecosyst. Environ.* **2007**, *120*. [CrossRef]
47. Singleton, G.R.; Brown, P.R.; Pech, R.P.; Jacob, J.; Mutze, G.J.; Krebs, C.J. One hundred years of eruptions of house mice in Australia–A natural biological curio. *Biol. J. Linn. Soc.* **2005**, *84*, 617–627. [CrossRef]
48. Holmes, N.; Campbell, K.; Keitt, B.; Griffiths, R.; Beek, J.; Donlan, C.; Broome, K. Reporting costs for invasive vertebrate eradications. *Biol. Invasions* **2015**, *17*, 2913–2925. [CrossRef]
49. Markets & Markets. Rodenticides Market by Type (Anticoagulants, Non-Anticoagulants, and Others), by End User (Agricultural Field, Warehouses, Pest Control Companies, Urban Centers, and Others) & by Geography-Global Trends & Forecasts to 2019. Available online: https://www.marketresearch.com/product/sample-8289309.pdf (accessed on 28 February 2019).
50. Morgan, G.; Simmons, G. Predator-Free Rakiura: An Economic Appraisal. The Morgan Foundation. 2014. Available online: https://www.scribd.com/document/214023167/Economic-Appraisal-of-Predator-Free-Stewart-Island (accessed on 28 February 2019).
51. Russell, J.C.; Broome, K.G. Fifty years of rodent eradications in New Zealand: Another decade of advances. *N. Z. J. Ecol.* **2016**, *40*, 197–204. Available online: https://www.jstor.org/stable/26198751 (accessed on 28 February 2019). [CrossRef]
52. Bassett, I.E.; Cook, J.; Buchanan, F.; Russell, J.C. Treasure Islands: Biosecurity in the Hauraki Gulf Marine Park. *N. Z. J. Ecol.* **2016**, *40*, 250–266. [CrossRef]
53. Masuda, B.M.; Jamieson, I.G. Response of a reintroduced bird population to rat reinvasion and eradication. *N. Z. J. Ecol.* **2013**, *37*, 224–231.
54. Bagasra, A.; Nathan, H.W.; Mitchell, M.S.; Russell, J.C. Tracking invasive rat movements with a systemic biomarker. *N. Z. J. Ecol.* **2016**, *40*, 267–272. [CrossRef]
55. Esvelt, K.M.; Gemmell, N.J. Conservation demands safe gene drive. *PLoS Biol.* **2017**, *15*, e2003850. [CrossRef] [PubMed]
56. Kardos, M.; Shafer, A.B. The Peril of Gene-Targeted Conservation. *Trends Ecol. Evol.* **2018**, *33*, 827–839. [CrossRef] [PubMed]
57. Lunshof, J.E.; Birnbaum, A. Adaptive risk management of gene drive experiments: Biosafety, biosecurity, and ethics. *Appl. Biosaf.* **2017**, *22*, 97–103. [CrossRef]
58. Estévez, R.A.; Anderson, C.B.; Pizarro, J.C.; Burgman, M.A. Clarifying values, risk perceptions, and attitudes to resolve or avoid social conflicts in invasive species management. *Conserv. Biol.* **2015**, *29*, 19–30. [CrossRef]

59. Delborne, J.; Kuzma, J.; Gould, F.; Frow, E.; Leitschuh, C.; Sudweeks, J. Mapping research and governance needs for gene drives. *J. Responsible Innov.* **2018**, *5*, S4–S12. [CrossRef]
60. Evans, S.W.; Palmer, M.J. Anomaly handling and the politics of gene drives. *J. Responsible Innov.* **2018**, *5* (Suppl. 1), S223–S242. [CrossRef]
61. Kuzma, J. Risk, environmental governance, and biotechnology. In *Environmental Governance Reconsidered*, 2nd ed.; Durant, R.F., Fiorino, D.J., O'Leary, R., Eds.; The MIT Press: Cambridge, MA, USA, 2017; pp. 235–262.
62. Kaebnick, G.E.; Heitman, E.; Collins, J.P.; Delborne, J.A.; Landis, W.G.; Sawyer, K.; Taneyhill, L.A.; Winickoff, D.E. Precaution and governance of emerging technologies. *Science* **2016**, *354*, 710–711. [CrossRef] [PubMed]