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REVIEW

Considerations for the governance of gene drive organisms

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ABSTRACT

Governance is a broader and more flexible concept than statute-driven regulations as it incorporates components outside the latter's remit. Considerations of governance are critical in the development of emerging biotechnologies such as gene drive organisms. These have been proposed or are being developed to address public and environmental health issues not addressed easily by conventional means. Here, we consider how the concept of governance differs from statute-driven regulation with reference to the role each may play in the development of gene drive organisms. First, we discuss existing statute-based regulatory systems. Second, we consider whether novel risks or different concerns derive from gene drive organisms, concentrating on characteristics that contribute to public health or environmental risk and uncertainties that may affect risk perceptions. Third, we consider public engagement, outlining how existing statute-driven regulatory systems and other governance mechanisms may provide opportunities for constructive interactions. Finally, we provide some observations that may help address science- and values-based concerns in a governance space larger than that of statute-driven regulatory systems.

KEYWORDS

Gene drives; governance; regulation; risk; risk management; public engagement

Introduction/Summary

Vector-borne human, plant, and animal diseases pose persistent and sometimes intractable public and environmental health concerns. The decreasing efficacy and environmentally deleterious use of broad-spectrum pesticides to which resistance has developed have led to a search for alternative controls. The idea of biasing gene spread away from classical Mendelian inheritance was first articulated in 1968 by Curtis [1] who postulated that it could be possible to introduce and 'drive' a gene precluding pathogen transfer into a wild insect population using chromosomal translocation: '*Mutant genes can be imagined the presence of which in a pest population would be favourable to man, without being very deleterious to the insect.*' Only recently have precise methods of moving genetic information into and among genomes such as CRISPR/cas9 and related nucleic acid homed enzymes provided the opportunity to drive the inheritance of desired constructs, hence the term 'gene drive.' The potential use of organisms with gene drives as part of a public and environmental health strategy raises a number of important questions, especially with respect to their governance.

What is governance? UNESCO defines governance as

> … *structures and processes that are designed to ensure accountability, transparency, responsiveness, rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation. Governance also represents the norms, values and rules of the game through which public affairs are managed in a manner that is transparent, participatory, inclusive and responsive. Governance therefore can be subtle and may not be easily observable. In a broad sense, governance is about the culture and institutional environment in which citizens and stakeholders interact among themselves and participate in public affairs. It is more than the organs of the government*….. [2]

There are other definitions, but generally governance extends beyond statute-driven regulations to encompass both science-and values-based concerns.

Historically, much of the discussion around the governance of emerging biotechnologies has focused on the specifics of regulation, including identifying gaps, and to a lesser extent, overlaps, in regulatory systems. It has also focused on whether regulation is product or process-based, what serves to trigger regulation, and the nature and type of data and information required for regulatory decision-making. For the purposes of this discussion, we define the concept of 'regulation' as the statue-driven authority of a government to exercise oversight over a product or technology.

In the United States (US), most regulatory agencies operate under laws that require regulatory agencies to make 'science-based' decisions. These have

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been described in detail in the NAS[1] report Animal Biotechnology: Science-based Concerns (NAS) [3], and generally encompass impacts on human, animal, and environmental health. It is important to note that although US regulation is science-based, the risk analyses that lead to regulatory decisions contain value-based judgments. In general, these are *a priori* decisions to make decisions that in the face of uncertainty are protective of human or other animal health and the environment. Another group of concerns, which for the purposes of this discussion are referred to as 'values-based', deal with issues outside statute-driven criteria in the US, and encompass social responses to scientific concerns, as well as issues dealing with transparency, participation, economics, ethics, and other issues. There is an extensive literature that reports on these and other values-based concerns including in the fields of Science, Technology, and Society and Policy Studies. For a review of a number of these issues as they pertain to gene drive organisms see the recent special issue of the Journal of Responsible Innovation [4].

Science- and values-based concerns for gene drive organisms have significant overlap. How those concerns are addressed may depend on the nature of the underlying question being asked and the regulatory rubric under which they occur. For example, questions arising from potential spread of gene drive organisms, including concerns about the extent to which various portions of the public could be exposed, have significant overlap with concerns about whether risks and benefits accrue to the same populations. Some of these concerns require science-based analyses, and it is possible that the incorporation of questions and concerns from the public may improve the quality of overall governance relative to narrowly circumscribed governmental 'science-based' regulatory decision-making. Najjar et al. [5] have described such an approach for one particular application.

Gene drive organisms are now being proposed, and in some cases, are being actively developed for uses that range from control of plant, animal, or human pathogens to the eradication of invasive species and the preservation of endangered species (Table 1). To our knowledge, no gene drive organisms have been released outside highly controlled laboratory settings. There is a growing literature [6,7] on how biosafety should be addressed in the context of these laboratory settings, including one study that addresses the incremental movement of gene drive organisms to regions of the world where they may eventually be deployed [8]. These are discussed in more detail later in this paper.

[1]Prior to 2015, what is now known as the US National Academies of Science, Engineering, and Medicine (NASEM) existed as separate bodies: the National Academy of Sciences (NAS) and National Research Council (NRC), the National Academy of Engineering (NAE), and the Institute of Medicine (IOM). Citations listed in this paper reflect the status of the institutions at the time of publications were issued.

Nonetheless, the urgency of solving public and environmental health problems provides significant pressure to use such approaches. This urgency is coupled with the need to investigate risks associated with gene drive organisms, to explore mechanisms for effective public deliberation, and to determine whether and how regulatory structures can address those issues. Addressing these concerns requires the broader concept of governance instead of reliance solely on statute-driven regulation.

Risk, uncertainty, and oversight of gene drive organisms

Foresight is limited, especially for disruptive and largely unanticipated technologies such as CRISPR-based gene editing of organisms and gene drive organisms that employ that technology. Informed governance specific to those technologies or their products thus naturally lags behind. Early in development, data and information are limited, and there can be great uncertainty regarding both the extent to which these organisms will behave as anticipated or whether they pose public or environmental health risks. Lack of information may limit meaningful public interaction or lead parties with vested or cryptic interests to make exaggerated predictions of both benefits and risks, with pernicious effects on regulatory decision-making. Further, judgments regarding the extent to which existing statutory authorities are applicable to a specific product are unclear. Opinions regarding jurisdiction also may be under-informed and can be politically motivated [9]. Gene drive organisms present such a case.

In the following, we provide an overview of existing regulatory structures, primarily in the US. We also describe some the key issues that cause tension between science-based and values-based concerns in the face of the high degree of uncertainty that may lay the framework for adaptive governance approaches. By adaptive or recursive governance, we refer to approaches that, among others, explicitly identify sources of uncertainty, accumulate relevant data to decrease uncertainty, and employ the accumulated evidence to inform subsequent actions or decisions.

It is useful to have a basic understanding of existing approaches to governance and regulation. In general, oversight of new technologies and their products has focused on formal regulatory review and decision-making, what we term 'statute-driven regulation'. Regulatory systems in different countries differ in what serve as 'regulatory triggers' – the characteristic that determines whether something is regulated. Some, such as the Netherlands, regulate technologies, including gene drives [10]. Others, such as the US, regulate products regardless of how they are produced. For example, the US Environmental Protection Agency (EPA) regulates biopesticides regardless of how they are produced

Table 1. Examples of types of gene drive organisms and their intended uses: model organisms, proof of concept, and proposed gene drive organisms (adapted from NASEM 2016) [8].

Class	Species/Trait	Type of Drive	Status
Model organism demonstrating artificial gene drive; maternal- effect lethal underdominance	*Drosophila melanogaster*	Proof of concept expression of color	Demonstrated [9,10]
Production of resistant alleles, and study of durability		Population suppression by Medea	[10]
Model organism	*Saccharomyces cerevisiae*	Augmentation with color change	Demonstrated [11]
Management or prevention dengue, chikungunya, Zika or other viruses in humans	*Aedes aegypti* and *Ae. albopictus* carrying pathogens	**Suppression**; eliminate or decrease population of mosquitoes below some disease-propagating threshold	Demonstrated entymological endpoint in contained laboratory conditions [12]
Management or prevention of malaria in humans	*Anopheles spp.*	**Suppression**; eliminate or decrease population of mosquitoes below some disease-propagating threshold	Demonstrated entymological endpoint in contained laboratory conditions [13]
		Alteration to make insect gut inhospitable to *Plasmodium falciparum*	Intermediate GE mosquito [14]
Management of agricultural insect pests	*Drosophila suzuki (spotted wing drosophila)*	Medea element engineered from a *Piggybac* vector; miRNA toxin/antidote as in *D. melanogaster*	Long term cage experiments to assay durability when introduced to wild type populations [15]
	Tribolium sp. (flour beetle)		Demonstrated drives in genetically variable populations in laboratory containment [16]
Conservation of native Hawaiian song birds	*Culex quinquefasciatus carrying avian malaria parasite Plasmodium relictum*	**Suppression** to eradicate *C. quinquefasciatus* Alteration to render *Culex inhospitable to P. relictum*	Theoretical [17, 18]
Conservation of endangered birds or protection of native biodiversity on islands by extirpating rodent pests	*Mus musculus*; *Rattus rattus*; sex ratio disruption	**Suppression** to extirpate non- indigenous rodent populations	Early stage development of genetically engineered mice; [19]
			Studies on laboratory/wildtype mouse mating behaviors [20,21]
Expansion of disease- resistant populations of wild animals	Gene(s) resistant to face cancer in Tasmanian devils Lyme-disease resistant white- footed mice	**Alteration** by identification of resistance gene and driving it through wild populations	Theoretical for Tasmanian devils [22]; Concept in development for white footed mice, currently limited to cis-genic gene transfer [23]
Replacement of developed resistance	*Amaranthus palmeri* (Palmer amaranth)	**Alteration** by reestablishing susceptibility of glyphosate-resistant plants;	Theoretical
	Echinochloa colona (barnyard grass or jungle rice) glyphosate resistance	Suppression by altering sex ratio of plants [8	

because they meet the definition of a pesticide (i.e. '*…Biopesticides include naturally occurring substances that control pests (biochemical pesticides), microorganisms that control pests (microbial pesticides), and pesticidal substances produced by plants containing added genetic material (plant-incorporated protectants) or PIPs*' [11]. The systems cover research including leading up to the issuance of experimental use permits by evaluating data specific to the biopesticide being developed under their existing statutory authority and applicable regulations. Some regulatory mechanisms, including many of those under US laws, are constrained to make science-based decisions regarding commercialization, and include determinations of whether a regulated product is safe and does what it is intended to do based on scientific evidence. Other statute-based regulatory systems expressly consider values-based concerns (e.g. the Endangered Species Act in the US, and much of the regulation in the European Union (EU)), and may take into account such issues as societal benefit, ethics, economics, and other concerns, as well as the science-based concerns.

Regardless of the form that these regulatory systems take, they all require addressing science-based concerns, which as previously stated, intrinsically contain value judgments that may be cryptic to those unfamiliar with regulatory risk assessment [12] but in general, tend to be protective of public and environmental health. The science-based concerns largely would be dealt with in similar ways: case-by-case hazard characterization based on the nature of the gene drive being used and the organism bearing it, a set of potential exposure pathways (or containment strategies), the durability of the drive, an estimate and characterization of risk, including an explicit discussion of uncertainty, and strategies to mitigate any risks judged not to be 'insignificant'. How risk estimates and uncertainties are handled is a critical feature of regulatory decision-making. The extent to which controls are applied can be a function of the underlying governance systems, which Paarlberg (1999) has characterized as generating policies that range from precautionary to preventative [13], depending on tolerance for uncertainty. The result of these policies is to generate what has been referred to as the 'Goldilocks dilemma' [14] in which being too risk-averse prevents valuable products from reaching the market (Type 1 errors), and being insufficiently cautious can lead to actions that result in harm (Type 2 errors) [15].

With this framing, the dilemma is clear; the challenge is to determine where the 'Goldilocks fulcrum' should be placed to find a practicable balance between Type I and Type II errors. If the overall decision-making process were limited to criteria based only on scientific evidence, fulcrum placement would be a function of posing the appropriate risk questions and answering them to the extent possible. Ideally, answers to risk questions provide regulators with sufficient certainty to make decisions, which, if authorizing release, specify conditions for risk mitigation and the requirements for post-authorization surveillance. The latter can help to continue to narrow uncertainties and ensure that unanticipated adverse outcomes do not occur.

'Risk,' however, is defined, perceived, assessed, characterized, or mitigated differently depending on the segment of the population that will or expects to experience it, or otherwise has an interest in the product [16,17]. Moreover, risk tolerance may also differ among individuals or groups. Understanding how different segments of society characterize hazard and risk may facilitate communication and substantive engagement.

The Goldilocks dilemma (i.e. whether to err on the side of precaution or promotion) therefore does not capture where the fulcrum should be placed (e.g. how promotional or preventative a system should be) or how many levers should be involved in decision-making. Is it possible to combine both science- and values-based concerns in one continuous process, or are multiple interactions required such that different concerns have their own balancing systems? Can and should this dilemma be distilled to finding a 'sweet spot' for science-based decision-making while creating and encouraging opportunities for meaningful public engagement?

Any placement of a 'Goldilocks fulcrum' should be viewed within the regulatory or governance framework in which it found, which in turn can evolve over time. Some of us have proposed 'planned adaptation' as an approach to dealing with expected changes in scientific and technical knowledge, economic conditions, and political priorities that could shift any 'ideal' placement of the fulcrum. In this approach, institutions and processes make proactive commitments to anticipate the need for policy updates. Practically, this could mean a system in which authorizations or approvals are considered provisional, and strategies are developed to gather additional data and information to decrease uncertainties, for example through monitoring of marketing or imports [18–20]. It may be possible to tailor some of the concepts key to adaptive regulation to governance issues associated with gene drive organisms. Nonetheless, deciding what knowledge is relevant to gather and factor into governance to find a sweet spot at any given time remains a challenge.

Is a regulatory decision enough?

Previous attempts to govern emerging technologies from the printing press to the products of biotechnology [21] have demonstrated that dichotomous regulatory decision-making is not well suited to topics characterized by a high degree of uncertainty, complexity, and consequent controversy (i.e. emerging biotechnologies). The

Asilomar meeting[2] on recombinant DNA (rDNA) research is often cited as the paradigm for the self-regulation of scientists. Although it resulted in regulatory frameworks that derived from the identification of science-based risks, it did not emphasize the values-based concerns that began to be primary foci of public concerns related to rDNA technology and its products.

A recent example in which a science-based regulatory decision demonstrates the scope of extra-regulatory governance can be found in the case of the approval of the rate-of- growth-enhanced AquAdvantage Salmon (AAS), produced by AquaBounty, Inc.).[3] Despite regulatory approval in two countries after rigorous science-based review accompanied by public comment, the commercial sale has either been blocked or has been met with opposition from either the other branches of the government (Congress in the US) or consumers (Canada). The stated reasons for the opposition coalesced on some science-based concerns, such as the potential for escape and interbreeding with Pacific salmon, or the desire for mandatory labeling of the food as being derived from a genetically engineered (GE) organism. Both the US [22] and Canadian [23] approvals addressed the issue of escape and interbreeding with other salmonids and found neither to pose a significant risk; at the time of approval, mandatory labeling could not be compelled under existing US [24], or Canadian law [25].

Although this example is for a GE organism from which food is derived, and may not be directly applicable to gene drive organisms, similar concerns may exist in both cases. Attitudes towards food products from GE sources vary greatly, often driven by concerns or perceptions of benefit and risk, as well as by other issues including whether similar outcomes could be reach by non-GE methods, whether the products were sold by large multinational corporations, and whether the public would derive an immediate benefit from the technology. Although some of these points may apply to gene drive organisms, the organisms are largely being developed for environmental (e.g. eliminating invasive species) and public health (e.g. eliminating vector-borne diseases) purposes, tend to be funded by philanthropies or public health organizations, and often are pursued by university scientists or non-profit organizations.

Nonetheless, actual public responses are difficult to anticipate, particularly given the additional efforts that technology developers are applying to engage members of the public in an *ante hoc* manner, or what some scholars have referred to 'responsible research and innovation (RRI)' [26].

Thus, focusing the Goldilocks fulcrum strictly on science-based regulatory decision-making overlooks opportunities for developing extra-regulatory mechanisms to address values-based concerns that may influence whether and how gene drive organisms are developed, reach regulatory decision-making, and possibly are deployed. In addition, because social and cultural values are expressed in different qualitative terms from health or environmental risks, there are often difficulties in melding the two types of concerns [27].

This lack of ability to incorporate both science- and values-based concerns is particularly important for gene drive organisms because some constructs are intended to have global spread, while others are intended to be local or attenuated. There have already been framing discussions of gene drive organisms as 'genetic extinction technologies'[28], implying that all gene drives are intended to be global and intended to suppress populations.

By providing opportunities for engagement that are not directly linked to regulatory decision and moving to a more expansive regulatory governance space, it may be possible to provide consideration of multiple inputs and address various issues associated with the introduction of these products. Employing such approaches may alter the framing of the Goldilocks dilemma from a scale between two boundaries to a more multi-factorial processes. It is interesting to speculate whether such processes could have altered the response of the legislative branch of the US government (which can be very responsive to some constituencies) or of Canadian consumers in the case of the AAS salmon.

Science-based concerns for gene drive organisms

Defining 'Risk'

Although most science-centered regulatory decisions are based on some definition of risk, different

[2]An early modern attempt at characterizing the Goldilocks fulcrum addressed potential outcomes of recombinant DNA (rDNA) research, and resulted in a voluntary moratorium on research until such risks could be discussed among the scientific community. The Asilomar meeting held in 1975, recommended that a Recombinant DNA Advisory Committee (RAC) be formed to provide guidelines for safety under the auspices of the National Institutes of Health (NIH). The resulting NIH Guidelines for Research Involving Recombinant DNA Molecules has been updated several times, and still pertains to contained research involving genomes intentionally altered using modern molecular biology. The most recent version is the 2016 NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules https://osp.od.nih.gov/wp-content/uploads/2013/06/NIH_Guidelines.pdf, and does not expressly address gene drive organisms. A recent workshop (July 2017 https://osp.od.nih.gov/event/nih-guidelines-honoring-the-past-charting-the-future/?instance_id=39 examined the current biosafety oversight framework, and discussed its future direction for the emergence of new technologies and their products, expressly including gene drives.

[3]The AAS salmon is the triploid, all female Atlantic salmon that is intended for the production of food. At the time of the US approval, it was to be bred from a fertile diploid genetically engineered parent and a wild type Atlantic salmon on Prince Edward Island, Canada. After being processed to produce an all-female triploid population, eyed eggs were to be air-shipped to Panama, where they would be raised to market weight in land-based grow out tanks (not ocean nets). Fish would be harvested on site, processed at a nearby facility, and the resulting gutted fish, steaks, or fillets would be air-shipped for sale in the US. Following the US approval, AquaBounty petitioned the Canadian Government to extend their Canadian breeding facilities to include a grow-out facility (also in land-based tanks); this was approved.in the summer of 2017 http://aquabounty.com/aquabounty-expansion/. A subsequent approval of a supplemental application to raise fish in the US was made in 2018 https://www.fda.gov/downloads/animalveterinary/developmentapprovalprocess/geneticengineering/geneticallyengineeredanimals/ucm605681.pdf although there is still a Congressional prohibition against importation of the fish.

organizations have applied different definitions to scenarios or organisms that have been intentionally altered via modern molecular biotechnology.[4] Some of these have been incorporated into proposed discussions of risks arising from gene drive organisms, and are important for understanding how scientists and regulators think about risks associated with organisms with intentional genetic alterations. Again, many of these apparent 'science-based' risks intrinsically contain value judgments (e.g. concepts such as 'undesirable outcomes' are quite value-laden) [11] but differ from the 'values-based' concerns as defined and discussed subsequently in this article.

- The 2002 National Academies of Sciences report *Animal Biotechnology: Science Based Concerns* defines risk as '*the product of two probabilities: the probability of exposure, PE, and the conditional probability of harm given that exposure has occurred P(H/E), so that Risk R = P(E) x P(H/E),*' [29]. It is careful to state that not all harms can be known, and that the process of risk assessment be recursive and evolve as more data and information become available.
- In 2014, the World Health Organization (WHO) issued a guideline for conducting research on genetically modified[5] (not with gene drives) mosquitoes. Their definition of risk is '*an objective measure of the product of the likelihood and consequences of a hazard, defined within a prescribed set of circumstances. Risk is often described as a probability distribution of a set of consequences over a defined time period*' [30].
- The National Academies of Science, Engineering, and Medicine (NASEM) Report *Gene Drives on the Horizon* (the Gene Drives report) [31] derives its definition of risk from the ecological risk assessment context, also with a probabilistic component: '*Risk is the probability of an effect on a specific endpoint or set of endpoints due to a specific stressor or set of stressors where a stressor is any agent or action with the potential to alter a component of the ecosystems'*. Interestingly, the term 'effect' refers to both positive and negative outcomes, similar to the process under the National Environmental Protection Act's (NEPA) initial Environmental Assessment (EA) where the term 'impact' can have a beneficial or harmful effect.
- The most recent relevant NASEM report '*Preparing for Future Products of Biotechnology'* (the Future Products report [26]), which expressly identifies gene drive organisms as 'future' products states that risks '*are comprised of undesirable outcomes (what), the possibility of occurrence (how likely), and state of reality (ways the risk occurs in pathways)*' [32].
- The Mathematical Ecology Research Group at the University of Oxford (UK) [33] reprises the Gene Drives report's recommendation for an ecological risk assessment prior to the authorization of any organisms with gene drives, stating that '*An effective ecological risk assessment*[6] *should identify 'hazards' and accurately predict the 'risks' of harmful effects arising from those', where hazards are 'substances or activities with the potential to cause adverse effects'; hazard characterization involves 'identifying potential harms that might occur'; exposure assessment is the 'exposure of the population, species, habitat or ecosystem to the hazard by dispersal, gene flow and ecological interactions,' and risk characterization 'is the probability of a harmful effect occurring given the nature of the hazard and the extent to which people, animals, plants, and/or the environment are exposed'.* They provide the original simple formulation of Risk = Hazard x Exposure [34].

All of these (and other) risk definitions encompass the concepts of harm (outcome), exposure, and probability. The important question with regard to the regulation of organisms with gene drives, however, is whether such organisms pose *novel* risks. We believe that the NASEM Future Products report addresses this point succinctly:

> *For future biotechnology products in all degrees of complexity and novelty [including gene drives], the committee considered the risk-assessment endpoints related to human health or environmental outcomes, such as illness, injury, death, or loss of ecosystems function. It concluded that the* ***endpoints are not new*** *[emphasis added] compared with those that have been identified for existing biotechnology products, but the* ***intermediate steps***

[4]For the purposes of this article, 'modern molecular biotechnology' encompasses techniques or procedures, such as *in vitro* interventions, to study the underlying science governing life processes, or to alter organisms or their derivatives in order to make or modify products or processes for specific uses. We note that this definition has been made for the purposes of this article, and has no formal regulatory or policy status of which we are aware. It is a modification of the UN Convention on Biological Diversity (article 2) definition of biotechnology. https://www.cbd.int/convention/articles/default.shtml?a=cbd-02 (accessed 10/10/2017).

[5]In the United States, regulatory agencies are careful to use the term 'genetically engineered' to refer to organisms that have had their genomes intentionally altered using modern biotechnology, as it is the opinion of the science-based regulatory agencies that with the exception of a small number of wild sources (e.g. berries, nuts, seaweed, game) all agriculturally important species have been genetically modified by selective breeding or other means. Others use the term 'genetically modified' to describe organisms that have been genetically engineered. In this document, the term 'genetically engineered' will be used unless specifically citing another document in which the latter is used. At the time of this writing, there is significant discussion concerning whether organisms that have had their genomes edited in particular ways (i.e. what is referred to as 'allele transfer') fit the terms genetically engineered, genetically modified, or are a class unto themselves for regulatory purposes.

[6]The US EPA defines an **ecological risk assessment** as the process for evaluating how likely it is that the environment may be impacted as a result of exposure to one or more environmental stressors such as chemicals, land change, disease, invasive species, and climate change, and includes four stages: planning and scoping; problem formulation; analysis; and risk characterization.

> ***along the paths to those endpoints have the potential to be more complex, more ambiguous, and less well characterized.*** [emphasis added] [26] (p7).

Characteristics of gene drive organisms important for characterizing risk

Gene drives, or 'violations of Mendelian segregation' [35] in which offspring populations possess unequal distributions of parental alleles are present in natural populations, including t-haplotypes in *Mus musculus* [36]*;* MEDEA in red flour beetles (*Tribolium castaneum* [37])*;* Wolbachia, the parasitic bacterium inhabiting insects [38]; and cytoplasmic male sterility in plants [39], among others. Unless introduced into organisms for specific purposes (e.g. the introduction of Wolbachia as means of extirpating *Aedes albopictus*, which is regulated as a biopesticide by the US EPA [40]), in their natural state these gene drives are not subject to regulation. The observation of naturally occurring 'selfish genes' and the development of synthetic gene drives has been summarized ably by Champer et al. [41] and Burt and Crisanti [42]. This paper concerns synthetic gene drives, which are produced by the introduction of molecular constructs capable of self-propagation throughout a population with resulting biased inheritance. At this time, they are most commonly produced using the CRISPR/cas9 genome editor.

The following section describes types of synthetic gene drive organisms based on characteristics that may contribute to the risk(s) such organisms may pose. In broadest terms, proposed or existing gene drive organisms can fall into one of two overarching classes:

> **Suppression drives** are intended to extirpate or reduce target populations by driving a gene that reduces fertility or fecundity, or otherwise causes individual organisms to fail to mature or develop to reproductive functionality, or
>
> **Replacement** or **alteration** drives, whose aims are to alter the physiology of the target organism and its progeny for specific purposes.

These categories may also be consider in light of their intended spread:

> **Global drives** are intended to spread extensively throughout a geographic area or ecosystem, with no built-in mechanisms for geographic attenuation, and
>
> **Local drives** are intended to have limited penetration into a geographic area or ecosystem due to designed features that attenuate or halt introgression.

To date, although many gene drive organisms have been proposed, few have been developed to completion. In some cases, intermediate organisms containing one or more components of a gene drive have been constructed. The long-term durability[7] of any gene drive has not yet been demonstrated [43]. As of the date of this writing, no reports of functional gene drives have been reported in mammals. Table 1 summarizes some examples of the types of organisms that have been developed are being developed or have been proposed, beginning with model organisms and progressing through proposed gene drives in more complex organisms with long life cycles.

Key characteristics of gene drive organisms that may influence risk and help bound uncertainties present in both modeling and data-driven risk characterization include the following:

- **Rate of spread**: High threshold drives that would require the release of a sufficient number of individuals to comprise as much as 50% of the target wild type population to persist [44]. Conversely, organisms with low threshold drives would need to replace only a small fraction of the target population in order to spread and persist [41]. Taking these characteristics into account in any early modeling could inform risk or safety assessment and thus planning appropriate containment measures for field trials.
- **Fitness of the intended target population:** Gene drives can positively or negatively affect the fitness of the resulting organism in a particular environment, which may in turn, influence the rate of spread or persistence [45]. Taking changes in fitness into account in study design would be useful to determine the degree to which fitness in a particular environment can influence population prevalence and inform risk analysis.
- **Reversibility**: The degree to which the organisms can be removed from the environment, or the drive inactivated so that the resulting target population returns to its native phenotypic state is an important potential risk mitigation measure. This can be effected by developing (1) reversal drives in which a second release contains a molecular mechanism that cleaves out the initial drive [46]; (2) immunization drives that could mutate the molecular target of the molecular drive complex such that the initial drive would no longer propagate itself through the population [47]; or (3) introducing more fit wild type populations, or in the case of high threshold drives, replacement of the population with gene drives by the wild-type. Information on the extent to which a drive can be reversed, and the durability of the reversibility drive could be collected to help evaluate risk and to design studies to model these characteristics.
- **Attenuation:** The degree to which spread can persist in an ecosystem or a geographical area could be influenced by distributing functional portions of the overall gene drive among different sub-populations of organisms to be released, all of which

[7]Durability can be thought of as the phenotypic stability of a gene drive organism over time.

would have to be present in order for the desired trait to be propagated (e.g. daisy chain) [45]. Spread or persistence could be controlled by the successive loss or withdrawal of necessary components (attenuation) or via underdominance mechanisms [48]. Again, the extent to which each component of the suite of organisms is effective and durable could have a significant impact on unintended adverse outcomes or the success of the gene drive organism.

- **Loss of efficacy/durability.** At this time, one of the most important considerations in developing gene drive organisms and assessing their risk is the loss of efficacy/ lack of durability of the intended gene drive. This may arise from a mutation in the genome in either the rDNA coding region or the enzymatic component of the target animal such that the intended allele duplication does not occur. Among other reasons, mutations may occur as the result of error prone non-homologous end-joining (NHEJ) that would render the targeted allele 'resistant' to the further action of the nuclease [39,49]. Champer et al. (2017) have shown that such resistance can develop in the term line of *Drosophila melanogaster* in as little as one generation [39]. Unkless et al. [50] have developed a population modeling framework to study the role of lack of durability of CRISPR/Cas9 (CGD) gene drive constructs introduced into a wild-type population [50]. Their modeling has shown that a lack of durability (referred to as 'resistance to CGD') would arise inevitably against 'standard' CGD constructs due to the error-prone nature of NHEJ. They postulate that resistance would likely be overcome only if NHEJ were effectively suppressed, the fitness costs of the introduced construct (the driver) were completely dominant, or fitness costs of the driver were equivalent to any arising resistant alleles.

Further modeling of such potential effects, especially as more data become available on specific gene drive applications will be critical in informing risk or safety assessments. Appropriate risk mitigation attempts could take into account any decreased in uncertainty when planning field trials, or studies leading to potential field release resulting from the consideration of the development of resistance and the changes introduced to overcome that resistance (including estimations of fitness). A key point in the loss of durability is the genomic location of the inserted gene drive construct, as transcriptionally inactive portions of the genome have no selective pressure to maintain sequence fidelity, and mutations (not limited to gene drive constructs) may accumulate without noticeable loss of fitness [51]. To that end, a large, multi-institutional group [52] has been developing a 'reference genome' for *Aedes aegypti* that characterizes key loci important to developing either suppression or replacement competence or insecticide resistance.[8]

The other major mechanism contributing to the lack of effectiveness of a gene drive is the same as would be found in any target/eradication interaction, namely, random mutations in the pathogen population that allow for the selective survival of those individuals resistant to the eradicator (e.g. pesticide, herbicide, antimicrobial), and loss of the effectiveness of the intended effect of the proposed gene drive organism.

Gene drive oversight

To the best of our knowledge, organisms with gene drive systems have not yet been deployed due to self-imposed moratoria by investigators, the relative immaturity of gene drive organisms, and in the case of The Netherlands, specific regulation [9]. To date, few specific formal regulatory statements or policies advise or specify how to carry out either laboratory studies or field trials of organisms with gene drives responsibly. Several investigators, professional or scientific organizations, groups of academicians, and countries, however, have provided policy papers or other thought pieces on the need for regulations [53–57]. In general, these reprise the potential science-based risks associated with global unattenuated gene drives, outlining to various degrees, those that may be associated such gene drive organisms. Some publications from the academic or public sectors have proposed the development of norms under which research can be conducted responsibly, with initial focus on outlining practices to ensure that unintended release from highly contained laboratory conditions does not occur [58–63].

Many of the recommendations and requests build on existing guidelines or recommendations for genetically engineered mosquitoes or other animals, with the understanding as previously stated, that the exposure pathways and potential range of harms may be more complex or rapid due to the propagating nature of gene drives. Careful attention to these guidelines by researchers and biosafety officers, as described below, should help encourage responsible conduct of research on gene drive organisms.

Biosafety

Biosafety during the development process is a critical issue; institutions should ensure that appropriate

[8] *Ae. aegypti* has a very large and highly repetitive genome; attempts to produce a genomic map in which contiguous DNA sequences are anchored to a physical chromosome have proven to be problematic. This report claims to have overcome many of these obstacles to anchor the genome to the three *Ae. aegypti* chromosomes.

One edit didn't seem to make it in, and that may be an issue on my part. The text for Footnote H currently reads

Ae. aegypti has a very large and highly repetitive genome; attempts to produce a genomic map in which contiguous DNA sequences are anchored to a physical chromosome have proven to be problematic. The authors report they have overcome many of these obstacles to anchor the genome to the three Ae. aegypti chromosomes.

systems are in place where genome editing is occurring so that gene drives are not created inadvertently. This is likely best accomplished by ensuring that biosafety and other institutional officers are appropriately trained and vigilant, and that appropriate training and is made available to investigators prior to initiating research. Recently, Benedict et al. [64] have provided a set of recommendations on the containment and management of gene drive organisms in the laboratory phase to help avoid the accidental release of insects. These are based on more traditional arthropod physical containment (e.g. physical containment beginning at the NIH-recommended levels 2 and 3, appropriate devitalization and disposal of investigational animals) and extend to strain segregation, including genomic screening, to prevent accidental cross-breeding with other strains that may be in the same facility. They also include a recommendation that molecular constructs include visual markers that would facilitate the rapid identification of GE/gene drive organisms.

Moving to the development and trials of gene drive insects to regions where they may be deployed for public health reasons, Quinlan et al. [65], as part of the Target Malaria program, have proposed steps for the appropriate handling of GE/gene drive insects in sub-Saharan Africa. Although focusing on science-based considerations of safety, this group has been actively involved in capacity development including early and ongoing engagement among research teams and the public. They have replaced the term 'biosafety' with 'facilities readiness,' which encompasses three concepts. The first of these is compliance, intended to ensure that all statutory and regulatory requirements are met. The second, colony utility, is intended to ensure that GE/gene drive mosquitoes remain constant over time and among facilities so that results of studies are not confounded by differences in biological material. The final concept, defensible science, is comparable in concept to good laboratory or good manufacturing practices, and is intended to ensure that appropriate training, record-keeping, and safe handling during research and shipping are maintained. The goal of these three concepts is to provides '*clear, repeatable, reliable, and accessible evidence appropriate to the interests and concerns of various stakeholders, over the long term.*'

Public engagement and participation

'Engagement' has been characterized as *'Seeking and facilitating the sharing and exchange of knowledge, perspectives, and preferences between or among groups who often have differences in expertise, power, and values'* [30]. The WHO Vector Control Advisory Group (VCAG)'s Guidance Framework for Testing of Genetically Modified Mosquitoes [66] emphasizes the *need for continuous interactions* [emphasis added] between various components of the publics and those engaged in research and deployment of 'genetically modified' mosquitoes.[9]

This definition of engagement differs significantly from the largely unsuccessful 'knowledge deficit model' [67], initially adopted by scientists and technology providers, which assumed that the reason for the public's uncertainty, and in many cases, concern, regarding a technology or its products was due to a lack of information and perhaps, a lack of familiarity with science and scientific reasoning in general. The 'obvious' solution to this problem has been to provide more information to the public (i.e., to overcome the knowledge deficit) so that unknowns can be resolved and concerns alleviated. The anticipated result was that the public would share the scientists' or technologists' enthusiasm for the matter at hand, or if not, object to it on science-based grounds. This unidirectional approach repeatedly has been shown be less than effective as a vehicle for developing trust among parties. In fact, in some cases, additional information about a technological issue has been shown to exacerbate public mistrust, and increase the perception of risk [68]. Given the lack of effectiveness of the preceding decades of 'scientists' and 'the public' talking past each other, there is now general recognition that public engagement is necessary for what some may refer to as multidirectional communications flow and 'successful roll-out' or 'express opt-out' of products or technologies.

Many groups have called for the active engagement of the public to ensure social acceptance during the development of the technology, and not as it about to be deployed, including several pieces specifically addressing gene drive organisms [69–74]. Much public 'outreach' has been perceived to have occurred *post hoc*, once a product was nearing approval or had been approved or authorized, so that information did not reach the public during a product's formative stages, allowing for their input.

For example, Hartley et al. [75] have recently studied how university staff, comprising senior management, senior research support manager, outreach officers and academic researchers from STEM fields at a unnamed 'typical UK research-intensive university' responded to queries regarding how to conduct research responsibly. They begin with the precept put forward by Douglas [76] that scientists have two overarching sets of responsibilities: role-based, which refers to the ethical conduct of research [15] and general responsibilities which accrue to the public at large [76]. They interpret the latter to mean 'collective approach to questions including … how to think about innovation in terms of values rather than consequences, and how to institutionalise responsiveness to the public.' Although the different subgroups surveyed varied in their opinions regarding the benefits of early participation, Hartley et al. concluded that

[9]Although the 2014 Guidance Framework does not explicitly address mosquitos with gene drives, many of the issues raised by GM mosquitoes are very closely related. The VCAG is currently completing a similar Guidance Framework specifically addressing mosquitos with gene drives, anticipated to be issued in early 2018 (personal communication with FNIH).

scientific research should be open to participation from involved polities at the input phase, else that participation will default to the 'output' or *post hoc* side. Concern was expressed among the survey respondents that lack of participation at the input phase could reprise the significant public resistance to certain emerging technologies such as agricultural biotechnology products, particularly in Europe.

Several recent efforts have attempted to develop and improve engagement on the input side of emerging biotechnologies. Among these have been public-inclusive meetings such as CRISPRCon [77], the extensive outreach efforts of Esvelt and colleagues [5], Target Malaria [78], the Safe Genes Program [79], as well as three Sackler Colloquia on the Science of Science Communication held by the NASEM [80]. Although outside the field of gene drives, the recent international Human Genome Editing Initiative strongly stressed the role of transparency and participation [81]. Public engagement is a broad and developing discipline reviewed in the recent special issue of the Journal of Responsible Innovation; [4] some challenges of public engagement are presented later in this article.

Segmenting 'The Publics'

Previous discussions surrounding the interactions of technology providers (which include scientists) and other members of society have tended to bifurcate populations into 'scientists' (the technology developers and providers) and 'stakeholders' or 'the public' (those who exposed to the technology or its products by means other than their creation and may accrue any risks). The terms 'publics' or 'stakeholders' typically have been poorly defined and have often lumped together anyone who was not involved in the actual production of a biotechnology product, but who may have had an interest in, cared about, or could have been impacted by the product – in short, mostly non-scientists. Technology providers and science-based regulators tend to express concepts of 'risk' and 'benefit' in terms typically associated with answers to science-based risk questions.

Even if not expressed in the same 'units' as the health and environmental risk cited above, part of the solution to this problem for gene drive organisms may be in gaining a better understanding of the parties' concerns about social and cultural values. Part of the difficulty in having a meaningful engagement among parties has been illustrated by the NASEM Future Products report (2017) [26] which states '*Methods to incorporate social and cultural values into risk analysis are limited because they often cannot be put on the same scale as health risks, environmental externalities, and monetized costs and benefits*.'

A central challenge to resolving the problem of the lack of comparability of the types of concerns may begin with trying to understand who comprises the parties engaged in the discussions. The WHO VCAG Guidelines [82] divide the 'public' into two overarching groups: the first are the '**community**,' characterized as those individuals or populations who live within the trial (or eventual release) site, and who would be directly affected by the conduct of the project (although the extent of direct involvement (exposure) would be a function of whether the gene drive organism was intended to be global or attenuated). The second, much larger group contains '**third parties interested in the research activities**' and includes global or regional public health and international organizations, including governments; the United Nations and organizations under its umbrella; scientists and scientific organizations including those focusing on public health and infectious disease with links to field testing activities; individuals or groups who monitor the use of biotechnology products; those with competing approaches to the use of organisms with gene drives (or GE insects); and representatives or organizations interested in social equity, cultural norms, threatened or endangered species and their habitats.

The 2016 NASEM Gene Drives Report [31] has sorted the 'publics' into three groups for the purposes of gene drive organisms. These are nested within each other, and are distinguished based on the immediacy of physical impact that organisms with gene drives may have, which again is a function of whether the gene drive is global or attenuated. The first is referred to as '**communities'** or the groups of people (or other organisms) who live or work in sufficient proximity to a field trial or release site that they would have a '*real, tangible, and immediate interest in the project*.' The second group is referred to as '**stakeholders**' who are individuals or groups who have '*professional or personal interests sufficient to justify engagement, but may not have geographic proximity to a potential release site*.' In other words, these groups may not experience direct exposure to the organisms with gene drives, but are nonetheless profoundly interested in engagement. The third group, the '**public'** represent groups who '*lack the direct connection to a project that stakeholders and communities have but nonetheless have interests, concerns, hopes, fears, and values that can contribute to democratic decision making*'. It is not clear whether regulators (including international institutions that may make recommendations for the safe use of organisms with gene drives) physically removed from the area in which gene drive organisms may be released fit more appropriately in the 'stakeholders' or 'public' subgroups, or whether they tacitly belong to their own group.

Another assumption, and perhaps the one that most exacerbates polarization, is the unfortunate tendency to assume that there must be 'sides' in an engagement, that that individuals can only belong to one 'group', and therefore behave according to either their self-assigned or externally imposed cohorts. In fact, people are complex; their opinions, motivations, and actions may not

be derived from an arbitrarily or self-assigned cohort membership, and may not be consistent over time or issues. The implication of this observation is that effective engagement for any individual or group involved in engagement requires both talking and listening to individuals as people, not to assumed roles. To date, it is not clear how to overcome these human tendencies and develop formalisms to take into account good practices while appreciating idiosyncracies; further directed investigation and scholarship may provide some recommendations.

Navigating the public's concerns

Values-based concerns may be over-arching and applicable to any modern biotechnology or its products, and include apprehensions about ethical, religious, economic, and other matters, a general discomfiture with change, or perception of loss, or the extent to which it is appropriate for humans (particularly scientists) to employ modern technologies to recast organisms or ecosystems to suit their needs. Juma [11] cites prospect theory, or the perception that potential losses appear to exceed potential gains compared to the current situation (the reference point) as one reason for the hesitation to accept innovations. These arguments have been exemplified in the discussions surrounding human genome editing [83] and with some adjustments to account for species, may be applicable to gene drive organisms.

Other concerns voiced by the public can be case-specific, and include such economic or justice issues as how much an environmental or public health intervention will cost, who will pay, and whether the exposed population(s) will benefit from the technology or only bear the risks. In the case of malaria, the NASEM Gene Drives Reports uses as an example of justice concerns the fact the people most affected by malaria are in low income countries and are generally lacking in higher education. The power differential between the relatively wealthy countries or organizations that may develop or own gene drive technologies and the populations who may be exposed to them may add to the difficulties in making decisions or having open and forthright conversations. This may give rise to perceptions of a neo-colonial relationship between the technology provider and the exposed populations. There are also carry-over issues from the genetically engineered plant sphere in which concerns regarding the economics of multinational corporate ownership of products become important, although the extent to which these arguments will persist in a publicly funded project are unclear.

Experiments in engagement

There is a relative dearth of empirical studies of public engagement in emerging biotechnologies. Recently, Murray et al. [84] have conducted an evaluation of 'risks' associated with attempts to control dengue using *Wolbachia*-infected mosquitoes (and not gene drive mosquitoes, but the findings can apply to those as well). Instead of defining 'risk' as an outcome related to some science-based outcome, these investigators performed a risk analysis on a procedural outcome ('Don't Achieve Release'), that is the '*risk that release of mosquitoes would not occur within a set time frame due to logistical, regulatory, political, epidemiological, and community concerns*', and a relative risk outcome ('Cause More Harm') that expressly considers release of the *Wolbachia*-infected mosquitoes resulting in more harm than existing mosquito control methods. Using the results of workshops attended by academics, regulators, community members, and non-governmental organizations, the investigators concluded that iterative community engagement involving both technical and non-technical members of the community should play a significant role in obtaining project approval. They also note that existing regulatory structures may not be sufficient, or as we have pointed out previously in this article, have the necessary authority to consider all of the publicly desired components of an application. Such considerations may result in significant delay unless proactive steps are taken to gather knowledge earlier in the process. In addition, the investigators emphasize that individual and community perceptions can play important roles in informing both research and public engagement when new technologies are introduced. Importantly, this is particularly the case when modeling future human behavior, such as continuing individual-level mosquito control practices, and not relying on the release of *Wolbachia*-containing mosquitos to 'cure' the problem.

Esvelt and colleagues [5] have also engaged with the public in their development of a gene drive that could break the cycle of transmission of the etiologic agent for Lyme Disease. Although the project is still in early phases, frequent interactions with the residents of Martha's Vineyard and Nantucket, combined with expressly granting authority for control of the project to the residents seems to have resulted in a curious and engaged public, and minimal stated negative perceptions. At this time, the residents of have not yet decided whether to allow a field trial. Time will tell whether this approach will be successful, and whether it can be expanded to larger non-island areas populated with less well-educated citizens.

Calls for and challenges of engagement efforts

Although the greater part of the literature encourages public engagement, there is some controversy over whether such interactions lead to a smoother and more universally satisfying path to decision-making for a technology or its products, or if it is possible, or even desirable, to develop a single system for accommodating both science- and values-based concerns (i.e. how to overcome the Goldilocks dilemma) [13].

The Future Products NASEM report (2017) [26] explored the effectiveness of public engagement, raising the issue of what level of control the public or any component of the public should have over the decision to deploy a technology. As previously noted, it cautioned that it is often not possible to include social and cultural values into the risk analyses employed by the US government due to the fact that these *values differ in kind* [emphasis added] from the more 'science-based' parameters. Nonetheless, it encouraged active engagement with the public, particularly early in the development of products, although it did not provide recommendations for potential venues or vehicles for such interactions. It also cites other NAS/NASEM reports in which the recommendations are made for more engagement.

Much of the literature on this topic discusses why engagement would be useful including ethical reasons; increasing the legitimacy of the decision-making process; and increasing the knowledge base on which decisions are made. The Gene Drives Report (NASEM 2016) [31] can be considered as a vehement recommendation to engage with the public in all phases of research, especially field trials, but again, does not provide recommendations for how to effect such engagements.

Jasanoff and Hurlbut [85] have recently proposed a mechanism that they refer to as a 'global observatory' for genome editing. Modeled in part on the Intergovernmental Panel on Climate Change, it is intended to provide opportunities to reframe discussions about genome editing to include more expansive input from different parts of society. This international forum is intended to serve as a repository and source of the global range of publications and positions on what we here have referred to as values-based concerns (e.g. policy statements issued by civil-society groups and formal bioethics bodies). It would also track and analyze positions and opinions ranging from setting research agendas to downstream issues such as patent rights. Part of the goal of this component would be to bring to light cryptic imbalances in power among societies. Finally, the observatory would serve as a '*vehicle for convening periodic meetings and seeding international discussion informed by insights drawn from data collection and analysis*'. It is worth noting that this forum does not require consensus-based decisions for its goals to be met. Although this short Comment published in Nature does not expand on how such a construct would be funded or where it might be housed, it does provide a preliminary proposal for nucleus around which science- and value-based concerns can be discussed.

Alternative perspectives on the topic of public engagements have been put forward. Kuntz [86] issued a response to the NASEM Gene Drive Report (2016) in which he objected to the shift of public engagement from 'sharing knowledge' to a 'mode of governance of research'. His primary concern is an ideological shift from 'Enlightenment values' to what he refers to as postmodernism. According to Kuntz, the latter posits that scientists cannot be trusted, and the 'their research must be subject to a democratic process, more precisely to a "participative democracy"'. Although Kuntz agrees that participation of non-scientists in research is a valuable tool in, for example, collecting data when the 'common goal' of all participants is more science-based data and information, his concern appears to be that engaging the public in upstream experimental design may interfere with scientific method or encourage acts of malfeasance on the part of some individuals. Examples cited for the latter include the experience of the French National Institute of Agronomic Research (INRA) which attempted to engage non-scientist stakeholders in discussions regarding genetically engineered vine rootstock, only to have field trials vandalized. In a previous study [87], Kuntz compiled a summary of field trials intended to provide data for risk assessment that were vandalized, including assaults on guards, predominantly in Europe. His general conclusion is that attempts at participatory engagement with the public are not always met with good faith, and that there are elements of the public willing to engage in unethical and criminal acts in order stop research on GMOs completely. Fagerstrom et al. [88] have also attempted to counter the arguments regarding the lack of safety of food from genetically engineered crops as perpetuating an overly precautionary approach on the part of the European Union 'caused and amplified by interested groups that are opposed to the technology and invest heavily into lobbying against it.'

More recently, the ETC group, an 'action group on **E**rosion, **T**echnology and **C**oncentration' obtained over 1200 emails from scientists in the United States under the Freedom of Information Act. The press release issued by ETC stated that '*the US military [specifically the Defense Advanced Research Projects Agency (DARPA)] is now the top funder and influencer behind a controversial genetic extinction technology [emphasis added]*' and that the Bill and Melinda Gates Foundation is using a public relations firm to '*stack key UN advisory processes with gene drive-friendly scientist, and …. counteract possible regulation*' [89]. Three days after the press release, the scientific journal *Nature* issued an editorial that stated that 'scientists must persist in pointing out the environmental dangers of gene editing', but the claims in the ETC press release was 'an unfair attempt to create damaging and polarizing spin' and that the 'emails reveal[ed] mostly mundane discussions about research and meetings' and that discussion relevant to the UN meeting 'discuss[ed] the UN process, [and] explain[ed] how scientists can share their expertise on the technology and its potential impacts. [90]

The editorial was clear to point out that individuals might see the impacts (on the UN process) differently, '*But presenting these exchanges as nefarious….only polarizes discussions …. and could de-legitimize scientists' role in*

the UN talks – one of the few mechanisms currently available for considering the implications of the technology from a global perspective'.

The conservation community has also encountered challenges in considering gene drive organisms. In 2016, the International Union for Conservation of Nature and Natural Resources held its quadrennial World Congress in Hawaii [91]. Gene drive organisms were discussed as potential means to arrest the predicted extinction of Hawaiian song birds due to avian malaria spread by mosquitoes, halt the spread of an invasive fungus that kills the ohi'a tree (a keystone species on the islands), and eradicate invasive rodents (rats and mice) that cause extinctions of native flora and fauna on the islands. These sessions were organized by a not for profit organization, Revive and Restore [92], whose mission is to 'enhance biodiversity through new techniques of genetic rescue for endangered and extinct species', and were sponsored by the National Geographic Society, with additional support from the American Bird Conservancy, the San Diego Zoo, the National Tropical Botanical Garden, and two agencies of the US Government's Department of the Interior, the National Park Service and the US Fish & Wildlife Service.

The Resolutions arising from the Conference address, among other things, two emerging technologies: the first calls upon the Society to

> *undertake an assessment …. to examine the organisms, components, and products resulting from synthetic biology …. which may be beneficial or detrimental to the conservation and sustainable use of biological diversity… and to recommend how IUCN, including its Commissions and Members, could approach the topic of synthetic biology and engage in ongoing discussions and deliberations with the synthetic biology community.*

The resolution immediately following the one addressing synthetic biology requests 'with urgency' that the Director General of the ICUN and Commissions

> *assess the implications of Gene Drives and related techniques and their potential impacts on the conservation and sustainable use of biological diversity as well as equitable sharing of benefits arising from genetic resources, in order to develop IUCN guidance on this topic,* ***while refraining from supporting or endorsing research, including field trials,*** *into the use of gene drives for conservation or other purposes until this assessment has been undertaken. [emphasis added]*

It is interesting to note that in the first, there is a willingness to engage with researchers, which appears to imply supporting or endorsing research, while in the recommendation for gene drives, there is an explicit prohibition even against research to determine what the risks associated with gene drive organisms might be.

The call for community engagement extends to publications intended for a non-scientific audience as well. A commentary describing gene drives as a tool for using either suppression or alteration drives to combat avian malaria has been published in *The New Yorker* [93], and calls on an 'informed society' to make the decision to proceed with the technology or not. Such calls, and the experience of the IUCN indicate that there should not be an expectation that engagement will lead to acceptance, but may result in different outcomes depending on the participants and the issue(s). Neither the *New Yorker* article nor do the other calls for public engagement provide recommendations for how those engagements should be held, who the informed society is, and what subgoups of that society should be afforded what degree of control.

Major programs considering the use of gene drive organisms

At the very early stages of the discovery and development of emerging biotechnologies, uncertainties, particularly those regarding safety and effectiveness, tend to be large. In the past, it has been incumbent on technology developers to address overarching uncertainties regarding outcomes or exposure pathways on a 'one-off' or case-by-case basis. These attempts are often unsatisfactory in resolving a general sense of concern, in part because they are limited to the application at hand and may lack generalizability. For example, the issue of whether making a specific Culex mosquito gut inhospitable to *Plasmodium falciparum* has an effect on the overall fitness of those mosquitoes in their native habitats may have general applicability to all Culex mosquitoes, or it may be specific to the strain in which the modification has been made. Without empirical evidence it is not possible to make that determination.

Funding efforts to address concerns beyond immediate applications may be difficult for several reasons. Public sector funding agencies may be reluctant to or unable to provide resources beyond proof of principle, especially if there is significant uncertainty whether regulatory agencies would be open to considering gene drive organisms. Research to address the uncertainties associated with safety, particularly if the results are intended to have general applicability, is rarely undertaken early in the development of products. This is likely because it is often beyond the remit of a federal funding agency, and private sector parties may be unwilling to expend resources that would benefit their competitors as well as themselves. Few recognize that very early on in the development of a technology, participants are more collaborators than competitors, as without the resolution of key uncertainties there is no market for any product. Finally, even in the public sector, few sources of capital have sufficient resources to fund uncertainty characterizations, and then provide the not-inconsiderable funds that required to address those uncertainties in a scientifically valid and statistically robust manner. There are, however, some indications that there is a willingness on the part of some governments or foundations

to consider gene drive organisms as part of a solution to large scale public or environmental health problems. It remains to be determined whether or to what extent governmental bodies other than those discussed below will fund the underlying risk research.

The Hawaii Invasive Species Council recently issued Resolution 17–2 [94] that states that standard insecticide tools may be insufficient to address the control of mosquitoes, and that the Council 'supports evaluation and implementation of technologies of landscape-scale control of mosquitoes in Hawaii, including sterile insect technique, incompatible insect technique, and genetic tools', while also encouraging *'researchers and management agencies to take a cross-sector approach to evaluating technologies … and support social science research to better understand the public concerns, attitudes, fears, and values related to mosquitoes, vector-borne disease, an native fauna,* and that the Council "*supports implementing evaluated technologies that are scientifically demonstrated as safe, effective control methods of mosquitoes*"'.

In December of 2016, the US Government held an Innovation Summit [95] regarding invasive species. Among the many conclusions and recommendations was that the regulators and the public need to prepare themselves for '*high-tech solutions to invasive species control including gene-based technologies*', while not ignoring '*low tech solutions such as risk analysis and horizon scanning approaches to improve targeting high risk invasive species and invasion pathways*'. In addition, the Innovation Summit emphasized the importance of social acceptance

> *strategically working to facilitate public understanding of emerging technologies and fostering the social acceptance that is necessary for technology application…. Public concern and resistance is already apparent for ….the development and release of biocontrol agents, and the use of genetic-based tools to eradicate populations of invasive species.*

The report further mentions 'citizen science initiatives to help build public understanding and acceptance…as well as fostering a sense of public ownership and pride for enacted solutions'.

An example of proactive engagement that has attracted the interest of several African countries is the Target Malaria project funded by the Bill and Melinda Gates Foundation and the Open Philanthropy Project [96]. Beginning as a university research program, it has grown to a multinational, multi-stakeholder project cooperating in Burkina Faso, Mali, and Uganda. It consists of several teams: a scientific team that is working to develop genetic controls for malaria in mosquitoes, a stakeholder engagement team whose assignment is working with local communities and national and international stakeholders (note that Target Malaria has not defined the publics in exactly the same way as the VCAG or Gene Drives Report have), a regulatory affairs team to ensure compliance with international, national, regional, and local regulations and to prepare data and information to meet those requirements, and administrative teams to help ensure coordination and timely completion. This project has a long timeline, and it is still early days, but the outcomes and lessons learned likely will have far-reaching implications.

Addressing overarching safety and security issues still remains a critical issue that may have some solutions in the relatively deep pockets of the federal government. In 2016, DARPA created a program called 'Safe Genes' [97] focusing on three technical objectives to improve the safety and accuracy of genome editing and gene drives: (1) *Control of Genome Editing* to develop gene drive constructs that provide spatial, temporal, or reversible control the gene editors; (2) *Countermeasures and Prophylaxis*, which provides 'treatment' options to improve the safety and accuracy of genome editing and gene drives, constrain the extent to which genome editors can operate within a genome, or to restore the edited genome to a state as close to 'wild type' as possible; and (3) *Genetic (Population) Remediation*, to purge unwanted engineered genomes from the environments into which organisms with gene drives have been released and restore them to as close to status quo *ante* as possible. In theory, the combination of complementary components of these three goals for any particular gene drive strategy could provide the multiple redundancies required to ensure appropriate biological containment in the event that a gene drive were to be deployed, as opposed to needing to 'retrofit' risk mitigation measures on existing applications. In July 2017, seven awards totaling approximately US $65 M were made to address these issues (see Table 2).

DARPA's Safe Genes Program facilitates interactions between federal, state, or other regulators and team members to develop appropriate risk questions so that data and information are developed to help inform governance and regulatory decision-making. Table 2 provides a summary of the specific goals cited by awardees. Each of these is will contribute to the state of knowledge so that recursive modeling can be based on data and information, and that risk analyses, including risk mitigation (e.g. technical safeguards including physical and biological containment) are based on empirical studies.

In addition to meeting technical milestones, DARPA requires each team to develop a plan to engage with the public, to work with independent experts to consider legal, ethical, environmental, dual-use, and responsible innovation (LEEDR) issues, and to ensure that teams have meaningful public engagement to help drive their technological developments. Awardees are responsible for determining how to engage with the public or, alternatively, how to study different forms of public engagement, and are encouraged to make their interim scientific and public engagement results available to the public. Study of these efforts may provide insights into how to conduct public engagement in other settings.

Table 2. DARPA Safe Genes Grant Awards and Summary Descriptions of Proposals (accessed from https://www.darpa.mil/news-events/2017-07-19).

Institution	Primary Goals
Broad Institute/Brigham and Women's Hospital/ Harvard Medical School	• Develop constructs to switch gene editors on and off in bacteria, mammals, and insects using model systems, the move to target organism that vectors malaria. • Develop general platform to identify chemicals that block genome editors to develop genome editors for therapeutic purposes by limiting off-target effects or protect against future biological threats • Construct synthetic genome editors for precision genome engineering
Harvard Medical School	• Create novel computational and molecular tools to develop precise genome editors capable of distinguishing between highly similar genetic sequences • Safeguard genomes by developing systems to detect, prevent, and reverse mutations that may arise from radiation exposure • Screen effectiveness of substances to inhibit genome editing
Massachusetts General Hospital	• Develop methods to control off-target genome editing as well as controlling and measuring on-target edits • Apply to mosquito gene drive systems over multiple generations • Develop strategies to control genome editors • Test gene drives in mosquitos in highly contained mesocosms resembling natural environments.
North Carolina State University	• Develop and test a mammalian gene drive system in rodents by targeting genetic variants found only in invasive animals • Expand tools to help manage invasive species threatening biodiversity, human food security, and zoonotic diseases. • Develop mathematical models of the behavior of such drives in mice; • test those models in highly contained but simulated natural environments.
Massachusetts Institute of Technology	• Develop self-exhausting 'daisy chain' gene drive platforms to disseminate and reversibly limit local sub-populations of organisms within a specific geographic region • Use nematodes as a model system • Transfer candidate systems to mosquito species capable of vectoring human diseases; refine systems in mosquitos
North Carolina State University	• Develop and test a mammalian gene drive system in rodents by targeting genetic variants unique to invasive populations • Expand tools to help manage invasive species threatening biodiversity, human food security, and zoonotic diseases. • Develop mathematical models of the behavior of such drives in mice; test those models in highly contained but simulated natural • environments.
University of California, Berkeley	• Develop novel, safe genome editing tools to use as antiviral agents models to target Zika and Ebola viruses • Identify proteins to inhibit unwanted (off-target) genome editing activity • Develop novel delivery systems for molecules effecting or inhibiting genome editors
University of California, Riverside	• Develop robust and reversible gene drives model system (yeast) • Transfer selected candidates to mosquitos vectoring human viral diseases • Develop molecular strategies to limit genome editing activity • Develop strategies to eliminate gene drives from populations via passive or active reversal • Develop mathematical models to inform design of gene drive systems and their mitigation

To the best of our knowledge, Safe Genes is the first program of its kind to devote this amount of effort not only for the development of products of an emerging biotechnology, but for the simultaneous development of risk mitigation and public involvement components. The results of these studies will likely have far-reaching implications for identifying what is known and what still needs to be researched to address both science-based risk questions and opportunities for public engagement. The results of this work could be validated if other countries or regions identified complementary activities and coordinated with the Safe Genes program to help resolve issues that may be applicable to their particular public or environmental health problems, as well as any social issues that are specific to their regions. Such activities may help to mitigate any carried over concerns regarding the funding source for the Safe Genes project.

Observations, implications, and considerations

In the preceding discussion, we have indicated that there are multiple points at which science- and values-based concerns have been engaged in the advisory, funding, discovery, and risk consideration phases of gene drive organism development. These phases comprise part of what is referred to as governance. Focusing these engagements at the regulatory decision-making phase, as has been the case with other then-emerging biotechnologies in the past, is not only too late, but at least in the US, falls outside much of the current legal authority granted to regulatory agencies. Finding other opportunities upstream of regulatory decision-making could help alleviate focusing positive and negative pressures on a single, or, at best, a very few actions by governments. More importantly, finding multiple, iterative, or adaptive opportunities for engagement with all parties involved may facilitate effective interaction and help build trust among individuals engaged or interested in gene drive organism development and potential deployment. It can also provide funders with a better sense of where to direct their resources, including the study and trials of mechanisms for engagement. Moreover, developing transparent governance frameworks can promote a synoptic and time-integrated participatory environment

that engages science- and value-based concerns. In turn, this can help remove the pressure for regulators to assume all of the responsibilities for public engagement.

Regardless of the underlying approach (product vs process), and surrounding governance frameworks, gene drive organisms will likely be evaluated on a case-by-case basis by regulatory bodies. In some cases, such as the US, the underlying policy is the regulation of products and not processes, and regulatory oversight is triggered by each agency's definition of a regulated article and not the process by which it has been produced. Oversight over early research, including highly contained laboratory studies, will thus comport with that agency's regulations and guidance in addition to any institutional safety oversight. In others, regulation is triggered by the process by which a product is made (or organism is produced), and guidelines or regulations from early research to potential deployment may be issued for the technology in general, rather than for specific products, although specific products would be reviewed on a case-by-case basis. As previously noted, there is a growing body of biosafety literature that addresses the actual nature of the confinement and containment that are recommended for early stage laboratory research.

Given that there appears to be some willingness to consider the use of 'genetic tools' in the solution of certain public and environmental health issues, individuals or organizations charged with or who are likely to propose solutions will likely advance a battery of options – that is, using all the tools in the toolbox. The implementation of some the tools in this toolbox, especially gene drive organisms, will require significant preparation and coordination among scientists, regulators, and the public at all levels and is likely to be impacted from the local to international levels. Resolving the Goldilocks dilemma, among other challenges, for gene drive organisms will require considerable effort, but the preceding discussion has demonstrated that there is a great deal of proactive activity in both the science and values- spaces.

Although the number of cases of early public engagement in the development of gene drive organisms is still small, and outcomes have yet to be determined, it is clear from previous experience with other gene-based technologies that later engagement and communications via the knowledge deficit model are not effective in establishing multidirectional engagement. In fact, they may be detrimental to product development and acceptance. Nonetheless, the uncertainties regarding the nature of effective public engagement can be considered to be just as important as the uncertainties associated with the more science-based risks. Just as some data indicate that there may be significant environmental risks associated with early field trials, there are also uncertainties regarding the effectiveness of early public engagement, particularly given the potential for carry-over from the strong negative opinions that some members of the public have for any form of genetic engineering, as seen in the work of Hartley et al. [25] Furthermore, there are few good models for how substantive engagement between technology developers and members of the public could occur most effectively.

The NASEM Future Products conclusion regarding risk should be re-emphasized: '[T]he endpoints are not new compared with those that have been identified for existing biotechnology products, but the intermediate steps along the paths to those endpoints have the potential to be more complex, more ambiguous, and less well characterized'. As one gene drive-specific risk assessment methodology will not be applicable to all gene drive organisms, these more complex and uncertain pathways will likely drive investigators and risk assessors to develop a set of risk questions specific to their particular applications that can be addressed in an iterative fashion. Possible approaches could include qualitative 'sensitivity analyses' to determine where the greatest contributions to risk exist. Mitigation measures can then be applied to decrease uncertainty or risk. The results of the Safe Genes program and the anticipated VCAG Guidelines on insects with gene drives will be useful in this respect.

Considering the existing uncertainty associated with gene drive organisms, a recommendation could be made that researchers should attempt to develop the most conservative (i.e. protective) construct possible. Esvelt and Gemmel [98] have urged that the default state of gene drives should be local and attenuated, and not global, unless a specific need for a global gene drive exists (e.g. for landscape scale solutions to otherwise intractable public or environmental health crises). As previously discussed, at this time gene drives do not appear to be very durable (see previous discussion), and even drives intended to be global do not persist beyond a few generations [39]. Nonetheless, it may be possible to override the loss of durability in the not too distant future, and due consideration should be given to ensuring appropriate safeguards during the development process.

The importance of funding organizations

Funding will continue to be a critical issue in developing safe and effective uses of gene drive organisms. Organizations considering funding such products are beginning to understand the extent of the commitment that underwriting such work for public or environmental health entails. Moreover, they are in a strategic position to support quality science and the additional governance that involves frequent interactions among the various polities identified in this article. Development programs do not end at proof of principle in the laboratory (or in highly contained environments); providing sufficient resources to conduct the more time and capital-intensive studies that move beyond contained

environments to semi-contained field trials and even trial open releases will become critical. To that end, the efforts by DARPA and Target Malaria should be commended and studied as examples of engaging proactively with these issues to guide further efforts in gene drive work and other genetic technologies that may emerge in the coming years.

When sufficient resources are made available, regulators and policy makers can interact with multiple technology developers and members of the public on issues of general concern outside the regulatory decision-making process which may be constrained by statutorily imposed confidentiality for individual applications. Such interactions can help develop internal capacity among the technology developers and regulators so that they can advise on how best to develop testing strategies that will help inform regulatory decisions. The implication of this is that the vehicles used to provide regulatory oversight should remain as flexible as possible, with primary early emphasis on ensuring safety, including containment and confinement, and effective engagement As previously mentioned, Jasanoff and Hurlbut [83] have provided a recommendation for genome editing; consideration may be given to whether a similar vehicle would be effective for gene drive organisms, perhaps starting with funding on a more modest regional rather than global level.

Recently, Emerson et al. [99], writing on behalf of 13 organizations that are sponsors and supporters of gene drive research (i.e. funders) have issued a set of five overarching 'guiding principles' that they propose be applicable to funders of gene drive research and the investigators who are engaged in such research. The guiding principles include (1) advancing quality science to promote the public good; (2) promoting stewardship, safety, and good governance; (3) demonstrating transparency and accountability; (4) engaging thoughtfully with affected communities, stakeholders, and public; and (5) fostering opportunities to strengthen capacity and education. They encourage other organizations to join them in supporting these guidelines. It is possible that such sponsors can provide an environment in which tools for harmonizing risk assessment methodologies, safety assessment, and capacity enhancement can occur to ensure that quality research is conducted under stringent oversight. Further they can help ensure that efforts at enhancing transparency and public engagement can be funded adequately.

Some of the applications of gene drive organisms are intended for countries or regions with limited capacity for scientific work, regulatory oversight, or even regulations. One key goal may be to increase capacity expansion to the regions in which testing and potential deployment is likely to occur. At least one program (Target Malaria) has received funding to develop gene drives in a region of Africa, and appears to be constructively sensitive to build a cooperative, sharing team composed of local and external participants. Potential activities that can be helpful in extending capacity include long-term scholarships in both hard sciences (e.g. molecular biology, entomology, population genetics, statistics, ecology) and in Science, Technology, and Society programs. The latter may help expand the dynamics of introducing emerging technologies to communities that may benefit from them, so that a more complete understanding of benefits and risks are internalized. Jointly, but not necessarily equally funded programs for capacity expansion may be exemplars for substantive engagement. These programs have the advantage of shared responsibilities for governance and thus avoid the perception of paternalism where knowledge of local customs may be limited. The contribution of funds from the impacted region or country ensures that those regions 'have a dog in the hunt', and exercise diligence over how their more limited funds are apportioned.

Considerations of the interplay of science- and values-based concerns in the governance of gene drive organisms

The urgency of a public or environmental health problem must be matched with efficient processes to facilitate decision-making. Rigorous project management can help ensure that appropriate studies are conducted in an expeditious manner if there is sufficient advance planning. Likewise, engagement does not have to be prolonged to be constructive and substantive. To the extent possible under existing laws, regulatory instruments (e.g. guidances, recommendations) can be written or amended so that decisions are staged and can be conditional on uncertainties being narrowed with accumulated data and information. These instruments can include specific *a priori* conditions for authorization withdrawal or, conversely, depending on data, loosening of restrictions. In some special cases, it may become imperative to write or modify new laws to accommodate exigent circumstances, although the track record for this has not been entirely positive. There may be lessons from the studies of adaptive regulation that can be specifically tailored to the governance of gene drive organisms.

Action in the face of urgency requires strong scientific underpinnings and ethical frameworks. Non-funding relationships may be of considerable utility in ensuring that adequate engagement occurs, especially if large area deployments are envisioned with a broad range of potential exposures. Deciding not to proceed with a gene drive organism intervention can be as valid an action as deciding to proceed. In particular, as part of their ethical responsibilities, producers of gene drive organisms should not over-promise their results, nor should others cast limited outcomes as grander designs that have not been met, especially given previous experience with the products of genetically engineered crops.

Returning to our earlier model, the placement of the Goldilocks fulcrum should be revisited as additional data and information become available, and as public engagement proceeds. Rather than thinking of the fulcrum as a point about which a teeter-totter pivots, a more accurate mental model may be a balancing point on which a disc is positioned, where equilibrium is achieved or the 'sweet spot' identified when the forces applied by science- and values-based concerns are balanced.

In closing, it is essential to recognize that many of the governance considerations that we offer are not entirely dependent on government regulatory decisions. There is a large governance space that exists before, during, and after regulatory decision-making that complements and reinforces government activity by providing vehicles that extend opportunities for research and engagement. This governance space, which some have called 'soft' (as opposed to the 'hard' statute-driven regulatory decisions) [100,101] involves funders, researchers, and various components of the interested or affected public. There is no settled opinion on how best to engage 'the publics', regardless of how they are defined. There are likely as many solutions as there are applications; some of these will be successful, others less so. What appears to be important is a genuine attempt from all parties to engage early, often, and honestly. We encourage the community of scholars and practitioners in this space to continue to explore options to fund science-based risk-related research, public engagement, capacity expansion, and constructive interactions. Many opportunities lie ahead for the advancement of strategies to develop gene drive organism applications in concert with multi-factorial engagement processes. We hope this paper has illustrated some key considerations and options to consider.

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