ENGINEERING THE WILD: GENE DRIVES AND INTERGENERATIONAL EQUITY

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ABSTRACT: New genetic engineering methods are allowing scientists to insert genes into organisms that have the potential to spread themselves throughout natural populations upon the release of individuals carrying those genes. Gene drive technology is being researched and developed for purposes of reducing or eliminating human, ecological or agricultural pest populations, or immunizing other desirable or endangered species against pests and disease. The ability of humans to alter populations within ecosystems through genetic engineering raises issues associated with biodiversity and conservation that, in turn, may affect the abilities of current and future generations to use and enjoy the benefits of the natural world. Yet, children and future generations are not typically given voice in legal, policy, or ethical debates. This article examines several of the intergenerational equity issues posed by gene drive technologies. A typology of gene drive purposes and their potential ecological impacts is developed, followed by an examination of how they may intersect with concerns about intergenerational equity. To our knowledge, this analysis is the first to explore human intervention through genetically engineering populations in the wild and the impacts on future generations.

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Most genetically engineered organisms (GEOs) approved for release into natural or agricultural environments are not expected to survive on their own for multiple generations either because they are less fit than the wild type or designed for human-managed systems. Confinement of the GEO and the introduced genes has been desirable for current applications of GEOs such as genetically engineered (GE) plants in agriculture or GE microorganisms for environmental pollution remediation. However, recently researchers have developed GEOs specifically designed to push or "drive" some of their genes into the natural populations.

Most genes in sexually reproducing species follow the laws of Mendelian inheritance; however, some break these laws based on a number of diverse genetic mechanisms that enable the genes to occur more frequently than the expected 50 percent of first generation offspring. Evolutionary biologists have

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been studying these naturally occurring "selfish genetic elements" for over 80 years, but only in the past decade have researchers synthesized genetic elements with these properties in the laboratory. One motivation for doing so has been to drive genes into pest populations that will make the pests more benign or reduce their density. Recently, there has also been discussion of driving protective genes into rare or beneficial species to preemptively shield them from chemical or biological stressors. Engineering these synthetic, "gene drive" systems took a leap forward with the recent development of site-specific genome engineering techniques based on CRISPR/Cas9 technology. CRISPR/Cas9 enables the engineering of multiple species with gene drives and greatly increases the ease and pace at which engineered organisms with drive mechanisms can be produced.[1]

The ecological and health risks and benefits of a specific application of a gene drive will depend on the species engineered, the type of alteration carried by the drive, the place where it is released, the strategy for release and monitoring, and the properties of the gene drive system itself. They will also be considered in the context of the contested history of agricultural biotechnology in the European Union, United States, and globally. Previous concerns about GE crops included direct impacts on human health and the environment, systemic changes in chemical use and other inputs, socioeconomic impacts on smaller and organic farmers, ethical issues associated with procedural fairness and choice, and cultural concerns.[2]

Some questions for thinking about these risks for each particular gene drive system and its release include the following: Is there a critical, high threshold of number of engineered individuals released (relative to the wild population) needed to enable the genetic construct(s) to spread? Does the construct(s) alter the characteristics of individuals in the population (ability to transmit pathogens), decrease population size, or both? Could the construct(s) cause extinction of the population or even the species, and is that desirable? Will the spatial spread of the construct(s) be self-limited? Will the construct(s) remain in a wild population or be lost with time? Is there a means for "recalling" (or eliminating) the initially released construct(s) by releasing other variants of the target species? What do the decline or changes in the target population mean for predators relying on that species? How does the decline or disappearance of a species affect ecosystem functioning or services? Could other more harmful species fill the ecological niches of the eradicated organ-

1. Kevin M. Esvelt et al., *Concerning RNA-Guided Gene Drives for the Alteration of Wild Population,* ELIFE, July 17, 2014, at 1, 8–9; Prashant Mali et al., *Cas9 as a Versatile Tool for Engineering Biology,* 10 NATURE METHODS 957, 957–63 (2013).

2. *See* SHELDON KRIMSKY & ROGER P. WRUBEL, AGRICULTURAL BIOTECHNOLOGY AND THE ENVIRONMENT: SCIENCE, POLICY, AND SOCIAL ISSUES 212–13 (1996). *See generally* Paul B. Thompson & William Hannah, *Food and Agricultural Biotechnology: A Summary and Analysis of Ethical Concerns*, *in* 111 ADVANCES IN BIOCHEMICAL ENGINEERING & BIOTECHNOLOGY 229, 229–64 (2008) (discussing the social and ethical concerns in using recombinant DNA); Michelle Marvier et al., *A Meta-Analysis of Effects of Bt Cotton and Maize on Nontarget Invertebrates*, 316 SCIENCE 1475, 1475–77 (2007) (discussing the ecological consequences of transgenic Bacillus thuringiensis crops).

isms, perhaps ones spreading even more detrimental human or ecological disease? What is the potential for horizontal gene transfer (HGT) of the gene drive system to other species and would the impacts be harmful to these populations or ecosystems?

Although the ecological risk assessment will be a key part of whether to release gene drives or not, there has been a push in the literature and among stakeholders for a broader framing of the issues that should be considered in governance and decision making about technological products. Some socioeconomic research and consultation has been conducted for projects involving the field selection and testing of GE mosquitos for population suppression,[3] but for gene drives, sociocultural and economic assessments for field testing or release are lacking. As an example of the importance of broader assessment, eradicating wild pigs in Hawaii using population suppression by conventional techniques was desirable from an ecosystem damage perspective, but Native Hawaiian communities rely on the feral pigs for cultural events and food, which causes a conflict between values of protecting ecosystems and cultural preservation.[4]

Although discussion of the societal issues for gene drives has begun in the literature, the media, and among key scientific and policy organizations, consideration of the potential consequences of gene drives for future generations has been virtually absent. Principles of intergenerational equity (IE) require that the wellbeing and desires of future generations be taken into account when making decisions for this set of powerful new genetic engineering technologies. Humanity's ability to alter populations within ecosystems through genetic engineering raises issues associated with biodiversity and conservation that, in turn, may affect the abilities of current and future generations to use and enjoy the benefits of the natural world. Furthermore, visions of the natural world may change over generations, and there are important IE issues to consider from a nonuse standpoint.

This article examines several of the IE issues posed by gene drive technologies. It reviews concepts and framings of IE that have been developed in other environmental policy arenas and then considers them for gene drives. It develops a typology of gene drive technologies and purposes to examine IE dimensions in more specific contexts. Finally, this article makes a proposal to incorporate principles of IE into contemporary decision making about whether, when, and how to deploy gene drives. To our knowledge, this analysis is the first to genetic engineering populations in the wild and the impacts on future generations.

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3. *See* James V. Lavery et al., *Ethical, Social and Cultural Considerations for Site Selection for Research with Genetically Modified Mosquitoes*, 79 AM. J. TROPICAL MED. & HYGIENE 312 (2008). *See generally* Janine M. Ramsey et al., *A Regulatory Structure for Working with Genetically Modified Mosquitoes: Lessons from Mexico*, PLOS NEGLECTED TROPICAL DISEASES, March 2014, at 1 (discussing the regulatory obstacles associated with suppressing mosquitos through genetic modification strategies).

4. Lynn A. Maguire, *What Can Decision Analysis Do for Invasive Species Management?*, 24 RISK ANALYSIS 859, 860–61 (2004).

I. INTERGENERATIONAL EQUITY AND ENVIRONMENTAL POLICY

IE arises out of arguments of equity for past, present, and future generations. It is based on the idea that all generations are partners in ensuring human survivability and well-being. Because goals and objectives of society extend beyond the current generation, as they cannot often be achieved in the present one,[5] each generation is morally obligated to support human continuity by protecting resources essential for life to ensure the dignity and well-being of Earth's current and future inhabitants.[6] Present generations are indebted to past ones for the resources that ensure their well-being and hold these resources in trust for the next generation. E.B. Weiss used the theory of "original position" in stating that "it is appropriate to adopt the perspective of a generation which is placed somewhere on the spectrum of time, but does not know in advance where," and that "a generation would want to receive the planet in at least as good condition as every other generation receives it and to be able to use it for its own benefit."[7]

E.B. Weiss articulates three basic principles of IE as the

> (1) conservation of options. "[E]ach generation should be required to conserve the diversity of the natural and cultural base, so that it does not unduly restrict the options available to future generations in solving their problems and satisfying their own values . . .";
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> (2) conservation of quality. "[E]ach generation should be required to maintain the quality of the planet so that it is passed on in no worse condition than that in which it was received . . ."; and
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> (3) conservation of access. "[E]ach generation should provide its members with equitable rights of access to the legacy of past generations and should conserve this access for future generations."[8]

She also suggests five duties of use:

> (1) the duty to conserve resources;
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> (2) the duty to ensure equitable use;
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> (3) the duty to avoid adverse impacts;
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> (4) the duty to prevent disasters, minimize damage, and provide emergency assistance; and
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> (5) the duty to compensate for environmental harm.[9]

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5. EDMUND BURKE, *Reflections on the Revolution in France* (1790), *in* 2 WORKS OF THE RIGHT HONOURABLE EDMUND BURKE 277, 368 (London, Henry G. Bohn 1855).

6. Edith Brown Weiss, *Climate Change, Intergenerational Equity and International Law: An Introductory Note*, 15 CLIMATIC CHANGE 327, 330 (1989).

7. *Id.*

8. Edith Brown Weiss, *What Obligation Does Our Generation Owe to the Next? An Approach to Global Environmental Responsibility: Our Rights and Obligations to Future Generations for the Environment*, 84 AM. J. INT'L L. 198, 201–02 (1990).

9. EDITH BROWN WEISS, IN FAIRNESS TO FUTURE GENERATIONS: INTERNATIONAL LAW, COMMON PATRIMONY, AND INTERGENERATIONAL EQUITY 50 (1989).

To favor the current generation by overusing or harming resources needed to ensure the well-being of future generations would violate IE.

Technologies deployed today will pose benefits, risks, and socioeconomic impacts to both present and future generations. Often these impacts are not known at the time of decision making, as is likely to be the case with the deployment of gene drives. Irreversibility of actions therefore becomes an important consideration for acting responsibly towards future generations. Indeed, IE has been most prominent when thinking about the use of environmental resources and human sustenance, and acknowledges that actions or inactions in the present can pose negative and sometimes irreversible consequences for future generations. Examples include the depletion of nonrenewable resources, long-term environmental degradation caused by polluting activities, and global warming. Today's decision makers are incentivized to act in a way that causes irreversible harm to future generations to maximize present benefits, as governance and political systems tend to favor current generations in decision making. For example, in regulatory policy, cost-benefit analyses are mandated for significant regulatory actions,[10] and using high economic discount rates in these analyses favor present over future benefits and decrease the present value of future benefits relative to the present value of costs for environmental protection.[11] Climate change prevention and mitigation are two areas in which IE has been an important consideration in international policy making and the choice of discount rate has been heavily contested.[12]

At the international level, the idea of IE has been incorporated into a range of treaties and cases. The Brundtland Commission of the United Nations in 1987 defined sustainable development as development which "meets the needs of the present without compromising the ability of future generations to meet their own needs"[13] and established the U.N. Commission on Environmental Development (UNCED). Many UNCED documents include reference to the concept of IE in their preambles.[14] For example, the preamble to the 1992 U.N. Convention on Biological Diversity encourages parties "to conserve and sustainably use biological diversity for the benefit of present and future generations."[15] The U.N. Framework Convention on Climate Change (UNFCC)

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10. Exec. Order No. 13,563, 3 C.F.R. 215 (2012), *reprinted as amended in* 5 U.S.C. § 601 app. at 101–02 (2006 & Supp. V 2011); Exec. Order No. 12,866, 3 C.F.R. 638 (1994), *reprinted as amended in* 5 U.S.C. § 601 app. at 86–91 (2006 & Supp. V 2011); Exec. Order No. 12,498, 3 C.F.R. 323 (1986) (revoked 1993); Exec. Order No. 12,291, 3 C.F.R. 127 (1982) (revoked 1993).

11. Daniel A. Farber & Paul A. Hemmersbaugh, *Shadow of the Future: Discount Rates, Later Generations, and the Environment*, 46 VAND. L. REV. 267, 278 (1993).

12. *See generally* Lawrence H. Goulder & Roberton C. Williams III, *The Choice of Discount Rate for Climate Change Policy Evaluation*, 3 CLIMATE CHANGE ECON. 1250024-1 (2012) (arguing that two discount rates apply in climate change policy).

13. World Comm'n on Env't and Dev., *Our Common Future*, at 24, U.N. Doc. A/42/427 (Aug. 4, 1987).

14. U.N. Conference on Environment and Development, *Rio Declaration on Environment and Development*, U.N. Doc. A/CONF.151/26 (Vol. 1), annex I (Aug. 12, 1992).

15. United Nations Convention on Biological Diversity, *opened for signature* June 5, 1992, 1760 U.N.T.S. 79, 145.

includes it not only in the preamble but also in the body of the treaty, stating that "[t]he Parties should protect the climate system for the benefit of present and future generations of humankind, on the basis of equity . . . ."[16] The U.N. Educational Scientific and Cultural Organization (UNESCO) put out a special declaration outlining responsibilities of the present generation to future ones and included in IE that future generations should have the freedom to also choose their own economic, political, and social systems.[17] This facet of IE is consistent with Weiss's "conservation of options" for future generations to solve their own problems.[18]

IE discussions surrounding sustainability and the environment have stressed utilitarian values, that is, conserving the natural world to preserve the option for future generations to thrive from it. Yet current generations must sustain themselves as well by using natural resources. In many cases, there is tension in whether one sacrifices the future to the present or the present to the future in resources utilization. Biodiversity protection is one area in which this tension exists. The importance in conserving biodiversity is often framed as utilitarian in nature to appeal to a wide range of stakeholders. For example, biodiversity is important for protecting ecosystem services in provisioning clean water, air, soil, and food. These services are important to current and future generations.

Less frequently heard are arguments for nonuse values associated with environmental and biodiversity protection in the context of IE. Weiss's obligations and duties neither stress nor preclude nonuse values. However, the obligation "conservation of options" includes the notion that values might change from generation to generation and that both natural *and cultural* resources should be preserved to allow for future solutions based upon a subsequent generation's "own values."[19] Regardless, much less discussion has focused on how conceptions of the natural world and desired states of it might change over time, and whether biodiversity protection extends beyond use-values in thinking about IE. In the context of gene drives and genetic engineering, these dimensions of IE might be particularly important. For example, does a GE species in the wild change nature away from a desired cultural state? Will future generations look upon GEOs in the wild as an asset, as a new type of "natural," or mourn losing the natural species? In summary, regardless of utility, what do gene drives imply for conserving options of future generations according to their cultures and views of nature?

Another component of IE extending beyond utilitarian arguments involves the reversibility of decisions today in the face of limited knowledge about their consequences. Norton formulated a conceptual tool, a "risk decision space," to

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16. Rep. of the Intergovernmental Negotiating Comm. for a Framework Convention on Climate Change, at 5, U.N. Doc. A/AC.23718 (1992).

17. Declaration on the Responsibilities of the Present Generations Towards Future Generations, G.C. Res. 31, U.N.E.S.C.O., 29th Sess., U.N.E.S.C.O. Doc. 29 C/Res. 31, at 44 (Nov. 12, 1997).

18. Weiss, *supra* note 6, at 330.

19. *Id.*

help identify adverse consequences that warrant priority attention because of their intergenerational aspects.[20] In the two dimensions are a degree of severity and a degree of reversibility; and those choices in the high category on severity and low on reversibility (high on irreversibility) fall into a distinct tier and require special attention to future generations.[21] He argues that economic and tradeoff analysis would not apply to this decision space, as the obligations to future generations should not be negotiated regardless of the present cost of mitigation and should be "governed by non-negotiable constraints."[22] Outside of the high-severity/high-irreversibility space, in a separate tier would be decisions for which economic criteria, or utilitarian cost-benefit analysis, would be appropriate and decisions could be governed by economic tradeoff analysis.

Although IE has been prominent international policy making in areas of climate change and sustainability, it is seldom discussed in the context of genetic engineering of species destined for environmental deployment. This article serves as groundwork for these conversations by focusing on the emerging area of gene drive technology. Because gene drive applications have multiple purposes and methods, first a typology of gene drives is developed to enrich the examination of IE issues. Then, the utilitarian and nonutilitarian dimensions of IE are summarized according to the purposes of gene drives. Questions addressed include the following: (1) How would the deployment likely affect the ability of future generations to use the natural world to ensure its own health and well-being? (2) How would the deployment affect the ability of future generations to apply their own values to enjoy or appreciate the natural world? and (3) How reversible is the deployment so that future generations could apply their own values to restore their options for use or nonuse decisions? Finally, a proposal is made to incorporate IE considerations into contemporary policy making for gene drives.

II. PURPOSES OF GENE DRIVES AND IE ISSUES

Gene drives to suppress insect populations have been proposed for over a decade.[23] However, the ease and versatility of their development has been greatly enhanced with the advent of new molecular engineering systems. In 2014, Esvelt and his coauthors described the development of CRISPR/Cas9 RNA-guided systems that can be designed to mutate, replace, knockout, or add virtually any target gene to specific sites in the genome.[24] Cas9 is a protein that cuts DNA (nuclease) that is part of acquired-immune systems in bacteria. It allows the cells to 'remember' the sequences of viral genomes that infect them by recognizing and cutting those sequences if they detect them again. DNA fragments from viruses are transcribed to produce RNAs with the same se-

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20. Bryan Norton, *Sustainability, Human Welfare, and Ecosystem Health*, 1 ENVTL. VALUES 97, 101–02 (1992).

21. *Id.*

22. *Id.* at 102.

23. *See generally* Austin Burt, *Site-Specific Selfish Genes as Tools for the Control and Genetic Engineering of Natural Populations*, 270 PROC. ROYAL SOC'Y B 921 (2003).

24. Esvelt et al., *supra* note 1, at 1–2.

quence, and the RNAs bind to and direct Cas9 nuclease to cut any matching DNA sequences, thus inactivating the virus in the genome. By genetically engineering the genes for this machinery, Cas9 can be directed to bind any guide RNA and cut any DNA sequence. After cutting, the host cell has machinery that will sometimes repair the cut or fail to do so, resulting in a mutated gene. However, in the case of gene drives, the cells can be directed to replace the sequence with another DNA sequence (or gene) of interest. For gene drives, the CRISPR/Cas9 system is directed to cut adjacent to its own recognition site and insert its own genetic code. Then, after the cut and during homologous recombination (chromosome pairing) in cell division, the CRISPR/Cas9 sequence is copied into the same site on the other chromosome, ensuring that each chromosome of the pair has a copy of the gene drive system. Therefore, all offspring inherit a copy. This means that the release of just a few individuals of a species can spread genes throughout populations under the right ecological conditions. These conditions include individuals coming together to mate and that possession of the molecular gene drive system does not have a detrimental effect on their fitness (e.g., the heterozygous individual resulting from the mating of an egg or sperm with a wild organism's egg or sperm has about the same fitness as the wild population). Gene drives are limited in effect to species that reproduce sexually, and their effects on populations will require several generations of mating to manifest. Therefore, species that have short life cycles and generation times are more ideal candidates for the application of gene drives.

The gene drive system can also be used to cut an essential or sex-linked (e.g., female killing at the larval stage) target gene in the organism so that the population declines; or it can be used to carry extra "cargo" genes into populations to confer desirable traits. Theoretically, cargo genes can come from any species and be introduced into any host.[25] Specific purposes of gene drives are limited only by the traits that can be inactivated, replaced, or introduced. General applications for the use of introducing gene drives into populations in the environment that have been articulated include: eradicating vector-borne human disease; enhancing agricultural safety and sustainability; protecting threatened species, and controlling invasive species.[26]

Governance and IE issues associated with an enabling technology like gene drives are often dependent on specific categories of applications[27]; therefore, these areas of purpose will be used in this paper to analyze IE issues associated with gene drives. We further break down each of these four general areas into subcategories that are presented in Table 1 to better understand the range of IE issues. The subcategories relate to the effect of the gene drive on the organism into which it is introduced; that is, the drive can (1) immunize the species against a hazard or the ability to carry it; (2) decrease its fitness to suppress the population; (3) enhance the population with the gene drive in

25. *Id.* at 2.

26. *Id.* at 12–16.

27. Jennifer Kuzma & Todd Tanji, *Unpacking Synthetic Biology: Identification of Oversight Policy Problems and Options*, 4 REG. & GOVERNANCE 92, 106–07 (2010).

some way; or (4) make it newly susceptible to an external chemical or biological agent. In the sections below, we discuss IE issues according to the four broad purpose categories and discuss how the considerations might differ depending on the effect of the gene drive. Utilitarian arguments are a key focus, although reversibility and nonuse values of ecosystems are also considered in the sections below.

Table 1. Categories of Gene Drive Purposes and Effects

Effect on Population Carrying the Gene Drive*

General Purpose	Population Immunization	Population Suppression	Population Enhancement	Population Sensitization
Human disease eradication	Block *vector-species* from carrying disease	Drive down population of disease *vector-species* with genetic sterility mechanism.	Enhance fitness of *populations that prey on vector*	Make *vector species or disease agent* newly susceptible to safer chemical or biological agent
Agricultural safety and sustainability	Immunize *agricultural commodity* against disease	Drive down populations of *insect or other pests* with genetic sterility mechanism	Increase *commodity* abilities to thrive on fewer inputs; enhance fitness of *prey of pests*	Make *pests* newly susceptible to safer chemical or biological agent
Control Invasive species	Immunize *desirable species* against invasive species	Drive down populations of *invasive species* with genetic sterility mechanism	Increase fitness or predation abilities of *predators of invaders*	Make *invasive species* newly susceptible to safer chemical or biological agent
Protect threatened or endangered species	Immunize *endangered species* against disease	Drive down populations of *predators of endangered species* with genetic sterility mechanism	Increase fitness of *endangered species* towards any stressor	Make *predator species* newly susceptible to safer chemical or biological agent

*The species into which the gene drive would be introduced varies and is presented in italics for each category

A. Human Disease Eradication

Pilot projects to decrease mosquito populations carrying dengue fever virus using genetic engineering and population suppression have already been deployed in field trials in Brazil, Malaysia, Cayman Islands, and Panama. Genetic engineering is superior to sterilization by irradiation because of fewer unintended mutations that are deleterious to the survival of the insects. In the case of dengue, GE sterile males were released to successfully suppress the overall population by upwards of 90 percent in the local area.[28] However, the CRISPR/Cas9 system was not used to drive the sterility gene throughout the population, and instead, batches of sterile GE mosquitos needed to be rereleased to continue to suppress the population. With a gene drive, theoretically, releases could be done once to suppress a population, with the goal of eradicting the vector of dengue and the transmission of the human disease. In Australia, another project for combating human disease included immunizing mosquitos to prevent them from carrying dengue by introducing a

28. Shraddha Chakradhar, *Buzzkill: Regulatory Uncertainty Plagues Rollout of Genetically Modified Mosquitoes*, 21 NATURE MED. 416, 416–17 (2015); Peter Winskill et al., *Dispersal of Engineered Male* Aedes aegypti *Mosquitoes.* 9 PLOS NEGLECTED TROPICAL DISEASES, Nov. 10, 2015, at 1, 2.

bacterium that inhibits transmission of the virus.[29] Immunization and population suppression seem to be the two most likely scenarios for the use of gene drives for decreasing the prevalence of human disease.

IE requires that the condition of the natural resources be left to the next generation in a state no worse than the current generation received them. Thus, benefits and risks to ecosystems from deployment of gene drives are of particular importance. Suppressing a natural population might adversely affect ecosystems. Yet, at the same time, the current generation has the right to use the natural world and its resources for self-preservation, and so combating human disease seems to also be warranted. The two tensions of IE come into conflict in gene drives designed for human disease control. Furthermore, if these diseases can be eliminated or permanently reduced, the next generation would benefit from a human well-being standpoint.

From a utilitarian perspective, a careful assessment of the risks and benefits to both ecosystems and human health in the present and future seems warranted for this category and IE concerns. However, the uncertainties are enormous. Uncertainty stems from several dimensions: (1) the low, but nonnegligible, probability of horizontal gene transfer of a population suppression drive to a desirable or beneficial species resulting in its demise; (2) the ramifications of population reductions of the target mosquito on other species like predators; (3) the posssibility that another, more harmful species could fill the ecological niche of the mosquito; and (4) potential impacts on ecosystem services from reductions in the target population. Also, although release of GM mosquitos in field trials has been shown to reduce mosquito populations,[30] reductions of disease may not ultimately materialize, making the benefit to risk ratio low. Surviving insects, although fewer, might be better at transmitting disease, or other insect populations could move into the empty niche and be better at transmitting the disease.

Although international guidelines have been developed, risk assessment for population suppression of disease-carrying mosquitos is still fraught with uncertainty and largely involves speculation about probabilities and severities.[31] In limited field trials, it is nearly impossible to collect field data for potential harms and benefits of full-scale release. Field trials also do not mimic full use of the technology, and ecosystem impacts cannot be fully understood for several years or even decades after deployment.

When CRISPR/Cas9 gene drives are added to the equation of sterile insect technologies, changes to populations may be permanent or irreversible. For population supression, population density may be too low to ever recover or the population might be eradicated, and it would be too late to bring back the

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29. T. Walker et al., Letter, *The* w*Mel* Wolbachia *Strain Blocks Dengue and Invades Caged* Aedes aegypti *Populations*, 476 NATURE 450, 450 (2011).

30. Danilo O. Carvalho et al., *Suppression of a Field Population of* Aedes aegypti *in Brazil by Sustained Release of Transgenic Male Mosquitoes*, 9 PLOS NEGLECTED TROPICAL DISEASES, July 2015, at 1, 10–11.

31. B. MURPHY ET AL., RISK ANALYSIS OF THE AUSTRALIAN RELEASE OF *AEDES AEGYPTI* (L.) (DIPTERA: CULICIDAE) CONTAINING *WOLBACHIA* 70–72 (2010).

population if an unanticipated ecosystem harm occurred. For immunization, Esvelt and his coauthors describe ways that gene drives could be "recalled" or replaced with safer drive systems in the event of unintended risks[32]; however, these technologies are still conceptual, are likely to not be 100 percent fail-safe, and the machinery for any gene drive (the CRISPR/Cas9 mechanism) would still be left behind in the species.

Returning to Weiss's obligations of IE,[33] conservation of access and options could be violated by suppressing or eliminating a species with gene drives, as it would no longer exist or be as readily available to use or conserve. Adhering to duties of "avoiding adverse impacts" and "preventing disasters" under conditions of uncertainty and ambiguity about the risks and benefits also seems problematic. Given the possible irreversibility of gene drives, conservation of options in "conserving the diversity of the natural and cultural base" is violated by elminating the wild type species. Considering Norton's risk decision space,[34] would the irreversibility also mean that this category of gene drives falls into the special space where the tradeoff of the benefit of combating human disease for the harm that may stem from eliminating a species should not be considered?

Certain geographic confinement strategies might help to mitigate the potential risks of wiping out a species. The gene drive could be designed to only work in a certain geographic region or surrounding populations could be immunized with a gene drive to inactivate the suppression gene drive.[35] However, even so, full containment may not be achievable and may come with the necessity to immunize the surrounding population with another gene drive, thus still altering the wild type species permanently.

Nonuse values in the IE framework to be considered include the values of future generations toward having permanently engineered wild populations of the disease-carrying organism. Will future inhabitants of the planet view these species as wild ones? Will they cease to enjoy their surroundings if many species become genetically altered? An immunization effect on the population carrying the vector to prevent it from carrying the disease might pose fewer problems from an IE perspective when it comes to utilitarian purposes of ecosystems. The disease-carrying organism (like the mosquito) would not be reduced or eliminated, but simply changed in its ability to transmit the disease. It could still provide ecosystem services and would be preserved for the future. This approach may conserve access; however, the problem of having a different genetic makeup from the wild population still exists, as it would contain the immunizing drive, or at least the machinery for CRISPR/Cas9. Weiss's conservation of options and quality might be violated. Subsequent generations might place a higher value on having the naturally established population in ecosystems rather than the genetically modified one.

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32. Esvelt et al., *supra* note 1, at 9–10.
33. Weiss, *supra* note 6.
34. Norton, *supra* note 20, at 102–03.
35. Esvelt et al., *supra* note 1, at 10.

Again, would people in the future enjoy GMOs in their natural environment as much as native species? This question cannot be answered, and thus conserving the option to enjoy the native species seems important for all of the subcategories in Table 1. Ending human suffering from a disease in contemporary times and in future generations will need to be considered against environmental use and nonuse aspects of IE.

The issues become further complicated when gene drives for human disesase control using population supression are compared to the alternative of disease control using chemical pesticides, which can be very detrimental to the environment, human health, and ecosystem services. Gene drives might come out more favorably from a ecosystem access and quality standpoint. However, if gene drives are compared to pesticide alternatives, they should also be compared to other older technological alternatives like intensifying research and development for human vaccines against the disease in question, or nonchemical vector control methods (netting, traditional biological control).

B. Agricultural Production, Safety, and Sustainability

The second general purpose category of gene drives also involves benefits to current generations in the production of greater amounts of food or safer food. Using gene drives for more sustainable production of food could also carry benefits for ecosystem health for generations to come, much like the human disease category. Both categories have the potential to reduce or replace the use of chemical pesticides in the environment. For example, gene drives can be used to reduce or elminate agricultural pests through population supression effects. Diamondback moths genetically engineered with female-killing systems have been recently tested in field cages in New York state.[36] Although these moths did not have a gene drive system and would have to be rereleased to sustain population supression, CRISPR/Cas9 systems are being tested in laboratories around the world for pest eradication.

Based on utilitarian perspectives, many of the IE questions for human disease control with population suppression would be the same for population supression of agricultural pests. However, the human disease benefit is not as apparent with agricultural pest suppression unless the agricultural disease agent could also affect humans (e.g., zoonotic diseases). The environmental benefits of replacing pesticides could be greater. The ecological risk questions would remain with population suppression; if the agricultural pest occupies an imporatnt ecological role, population suppression may adversely impact future generations' abilities to use the ecosystem services they provide. Predator species could also be lost, and other harmful pests could fill the niche once occupied by the agricultural pest.

In comparing gene drive effects for this category (see Table 1), because population supression would likely have the benefit of chemical use reduction for food production, using gene drives for this purpose might protect the environment more than making the pests more susceptible to chemical agents

36. Devin Powell, *Replacing Pesticides with Genetics*, N.Y. TIMES, Sept. 1, 2015, at D3.

through gene drives (see column 4 in Table 1). However, the economic incentives might tilt the balance towards gene drives for chemical susceptibility, as the agricultural industry has developed products in the past with which chemicals were paired as a revenue-generation strategy. These products have ultimately increased the use of chemicals (e.g., GE herbicide tolerant crops and herbicides like RoundUp). In contrast, developing gene drives for pest suppression would not be of great economic benefit to the developers, as the goal would be to release them once and once only for eliminating the pest in the target area. Again, careful risk-benefit analyses for gene drives for agriclutural pest protection would be needed and should be compared to several alternatives. Taking a longer-term perspective for future generations might tip the balance in favor of genetic approaches over chemical approaches, especially if the pest is also an invasive species (see category below), as population suppression with gene drives could not only reduce pesticide use, but actually benefit contemporary and future generations by protecting ecosystem quality and access for the future by ridding it of an invasive species.

Another option for this category is to immunize the agricultural commodity against the disease through a gene drive system. Most commodities would not have the short generation times needed for this option to be feasible nor would they sexually reproduce in the wild. Seeds and breeds of animals are often purchased from companies to ensure quality. Hybrid corn is a prime example of a commodity crop that has been bred for important traits over many generations. However, if the crop were one with short generation times and open pollination or crossbreeding, immunization strategies could be pursued. Putting gene drives into food crops would likely meet public resistance, and risks of human consumption of the engineered crop with the gene drive could be viewed as posing an unacceptable risk regardless of how small the probability of transferring that gene to a human germline cell would be. IE issues here might include human well-being in the future, given the dread and unfamiliarity with the technology and uncertainties surrounding the risk of horizontal gene transfer to animals and humans.

Irreversibility (like the human disease category—either through population disappearance or genetic change) and different conceptions of "nature" across generations for this category seem to present similar issues to human disease eradication and gene drives. One difference would be that it might be more acceptable to engineer human-managed agricultural ecosystems in the open environment from a cross-generational cultural standpoint than to engineer unmanaged ecosystems.

C. Control of Invasive Species

Invasive species can wreak havoc on ecosystems, causing damage to native species, ecosystem services, and the ability of humans to enjoy nature. IE arguments may favor the use of gene drives to eradicate invasive species for ecosystem protection, as the current generation would be taking the action to conserve access, quality, and options for future generations to benefit from the natural world. For example, gene drives are being considered for applications to eradicate invasive mice on islands to protect native birds and ecosystems.[37]

Ecological risks still need to be considered, but would have less to do with the disappearance of the invasive species (seen as a goal and the ultimate benefit) and would have more to do with horizontal gene transfer of a population suppression drive into desirable species or the transfer through interspecies breeding. However, cultural and temporal contexts will need to be considered in relation to whether contemporary cultures have come to rely on the invasive species over time and about whether cultural heritages might be lost in future generations as a result of the invasive species eradication (see previous example of feral pigs in Hawaii).[38]

In this category, immunizing the protected species against invasives, making the invasive susceptible to a chemical agent, or enhancing predators of invasives through gene drives seem to present more potential ecological risks than simply suppressing the population of the invasive species. If population suppression is used, the invasive species simply goes away, whereas with the other strategies, the GEOs persist in the wild and could be seen as an affront to nature in future generations.

In summary, in contrast to the first two categories, there might be an imperative to use gene drives from IE standpoints, as the primary benefits are to ecosystems and a key goal of the effort is to protect ecosystems for future generations. Greater uncertainties and irreversibilities might be tolerated in this context before deployment, although the possibility of gene transfer to desirable species should be carefully considered.

D. Protection of Threatened or Endangered Species

Protecting threatened species by gene drives might be warranted from IE perspectives, as the goal is to conserve the species for future enjoyment and use. Especially if no other viable options are available, using gene drives to genetically alter the threatened species to protect it against disease or other environmental threats may be better than not having it at all in the context of future generations' values. Nonuse values of IE, such as potential negative cultural attitudes towards GE animals in the wild and inabilities to enjoy the engineered species, would still come into play. However, future generations would at least have the option to see the species and make this determination for themselves.

For example, native Hawaiian bird species are disappearing because of interacting elements of climate change and emerging mosquito diseases. Climate change has increased the presence of Avian-malaria-carrying mosquitos at higher altitudes, now the only remaining habitat for many bird species. Time is running out to protect the birds, and there seem to be no good

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37. Esvelt et al., *supra* note 1, at 15; *see also Conserving Island Biodiversity: Welcome*, N.C. ST. UNIV., https://research.ncsu.edu/islandmice/ (last visited Apr. 12, 2016).

38. Maguire, *supra* note 4.

alternatives.[39] Gene drives could be used to adapt the birds to alternative habitats (population enhancement), immunize them against malaria (population immunization), or eradicate the mosquito pest (population suppression).

For population suppression of the mosquito, ecological risks would be similar to the purpose category of human disease control from population suppression (see above, Section II.A). An important ecological risk that should be considered for population enhancement or immunizing the threatened species would be unintended harm to the protected species from introduction of the gene drive which could cause it to disappear even more quickly. For example, gene drives might cut the genome of the organisms in what are called "off-target" sites, thus potentially disrupting genes that are important for survival. Off-target mutations from CRISPR/Cas9 are quite likely[40] as the guiding RNA designed to bind the target site can also bind to other sites on the DNA with some homology, albeit not as frequently or strongly. CRISPR-Cas9 gene drive technology is also designed to be active over many generations, and with every generation, the chance of mutation at off-target sites increases.[41] Unanticipated harm through off-target mutation can come to other species that are sexually compatible to the threatened species or to any species through horizontal gene transfer.

Ecological risk and benefit analysis, taking into consideration the conservation of options, access, and quality for future generations, is important for this category as well as the previous ones. It seems that in cases where the species is rapidly disappearing, not doing anything will harm the ability of future generations to use or enjoy the natural world more than the use of gene drives to protect the species and the ecosystem services it provides. Current generations might need to accept the irreversibilities and the potential violation of nonuse values in the future to simply keep the species on Earth for posterity.

III. DISCUSSION AND SUMMARY

This article is a first step to broadly examine several issues associated with intergenerational equity and gene drives. More scholarly work will be needed to analyze the IE issues for case studies of gene drives combining a specific purpose, effect on target population, and geography. However, from the brief analysis within this article, we already can see how a one-size-fits-all policy for considering IE and gene drives does not work. Applications of gene drives to human disease and agricultural production seem primarily to benefit the current generation with secondary benefits and potential risks to future

39. Katie Langin, *Genetic Engineering to the Rescue Against Invasive Species?*, NAT'L GEOGRAPHIC (July 18, 2014), http://news.nationalgeographic.com/news/2014/07/140717-gene-drives-invasive-species-insects-disease-science-environment/.

40. Jeffry D. Sander & J. Keith Joung, *CRISPR-Cas Systems for Editing, Regulating and Targeting Genomes*, 32 NATURE BIOTECHNOLOGY 347, 350 (2014).

41. Bruce L. Webber et al., *Opinion: Is CRISPR-Based Gene Drive a Biocontrol Silver Bullet or Global Conservation Threat?*, 112 PROC. NAT'L ACADEMY SCI. 10565, 10566 (2015).

generations. In these cases, the irreversibilities and uncertainties surrounding the deployment of gene drives may not be acceptable from IE standpoints of conserving options, access, and quality. Deployment of gene drives should proceed cautiously and occur only if these uncertainties can be reduced with upstream ecological risk and benefit analyses and dialogue to envision the concerns of subsequent generations. In contrast, there seems to be more latitude, and perhaps even an imperative, to develop gene drive technologies for protecting threatened species and reducing invasive species. In these two categories, irreversibilities and greater uncertainties could be tolerated to conserve the natural and cultural world for future generations, especially if alternatives to gene drives are not viable.

Beyond analysis, there are challenges with incorporating IE into policy making. IE concerns seem absent from policy and regulatory discussions of GEOs in the United States. In the United States, most regulatory decision making about GEOs has been based upon the consideration of only direct environmental, human, or animal health risks, with little room for other harms, risks, and ethical or socioeconomic impacts to be considered.[42] The United States is also not a party to the Convention on Biological Diversity, which applies to Living Modified Organisms through the Biosafety Protocol and considers IE in its preamble.[43] The U.S. regulatory system prides itself on being "science based," a phrase often used to dismiss broader social, cultural, or ethical concerns, and to highlight only direct health or environmental harms. Yet, "scientific" risk issues are fraught with value choices and dependent on the sociotechnical system in which they are embedded.[44] Furthermore, the history of GEO governance highlights the need for broader considerations. Social concerns about GE foods were not anticipated, and public skepticism, mistrust, avoidance, and demands for labeling have ensued. For human genetic engineering and gene editing, ethical dimensions have been more prominent in recent policy discussion, but for environmental deployment of GEOs, these considerations are not often allowed in mainstream policy debates. This lack of discussion will need to change if we are to carefully consider how genetically engineering wild populations with gene drives will affect future generations.

A formal regulatory policy stance on gene drives and oversight has not been taken yet, although the U.S. Department of Agriculture has exempted

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42. Inmaculada de Melo-Martín & Zahra Meghani, *Beyond Risk: A More Realistic Risk-Benefit Analysis of Agricultural Biotechnologies*, 9 EUROPEAN MOLECULAR BIOLOGY. ORG. REP. 302, 305 (2008).

43. United Nations Convention on Biological Diversity, *supra* note 15. The 1992 U.N. Convention on Biological Diversity, expresses the determination of the Contracting Parties "to conserve and sustainably use biological diversity for the benefit of present and future generations." *Id.* at 145.

44. Paul B. Thompson & Wesley Dean, *Competing Conceptions of Risk*, 7 RISK: HEALTH, SAFETY & ENV'T 361, 371–72 (1996); *see, e.g.*, Jennifer Kuzma, & John C. Besley, *Ethics of Risk Analysis and Regulatory Review: From Bio- to Nanotechnology*, 2 NANOETHICS 149 (2008).

several gene-edited crops from regulatory review.[45] This moment would be a good opportunity to consider the impacts releasing GEOs with genetic drives into the wild would have on future generations, as the U.S. Office of Science and Technology is in the process of reinterpreting and clarifying its federal authorities under the U.S. Coordinated Framework for the Regulation of Biotechnology (CFRB).[46] Advances in gene editing and gene drive technologies, as well as a greater diversity of GEOs and growing controversy over GE foods, have prompted this policy attention.

Meanwhile, the deployment of GE insects for population suppression is quickly advancing. GE diamondback moths have been approved by U.S. Department of Agriculture for field trials in the Northeastern United States to bring down populations of the pest, and a proposal by the company Oxitec (purchased by Intrexon) to use GE mosquitos for control of dengue in the Florida Keys has been submitted to the U.S. Food and Drug Administration for review under the agency's new animal drug authorities.[47] Oxitec has already field tested GE *Aedes aegypti* for dengue control in several lesser-developed nations and territories, such as the Cayman Islands, Panama, Malaysia, and Brazil, with some success in population reductions of the mosquito.[48] New concerns about the Zika virus potentially causing microcephalpy outbreaks in Brazil have prompted several mainstream scientists and media stories to call for the use of GE mosquitos for decreasing mosquito populations that carry the Zika virus.[49] At the same time, some advocacy groups have proposed that the previous releases of GE mosquitos by Oxitec in Brazil may have caused the new disease profile of Zika, as they co-occurred in the same general geographic area.[50] With increasing proposals for the use of genetic engineering in the wild, there is a strong argument to be made for consulting with the generations that are to inherit the world altered through this technology. Yet, children and future generations are not typically given voice in legal, policy, or ethical debates. While we wait for policy systems to change, a simple step in

45. Jeffrey D. Wolt et al., *The Regulatory Status of Genome-Edited Crops*, 14 PLANT BIOTECHNOLOGY J. 510, 515 (2016).

46. Emily Waltz, *A Face-Lift for Biotech Rules Begins*, 33 NATURE BIOTECHNOLOGY 1221, 1221–22 (2015).

47. Greg Allen, *Genetically Modified Mosquitoes Join the Fight to Stop Zika Virus*, NPR.ORG, http://www.npr.org/sections/goatsandsoda/2016/01/26/464464459/genetically-modified-mosquitoes-join-the-fight-to-stop-zika-virus (last updated Feb. 4, 2016, 2:26 PM).

48. Carvalho et al., *supra* note 30, at 5.

49. *See* Faye Flam, *Fighting Zika Virus with Genetic Engineering*, BLOOMBERG VIEW (Feb. 4, 2016, 10:00 AM), http://www.bloombergview.com/articles/2016-02-04/fighting-zika-virus-with-genetic-engineering; *see also* Allen, *supra* note 47.

50. *See* Mike Adams, *Zika Virus Outbreak Linked to Release of Genetically Engineered Mosquitoes . . . Disastrous Unintended Consequences Now Threaten Life Across the Americas*, NAT. NEWS (Feb. 1, 2016), http://www.naturalnews.com/052824_Zika_virus_genetically_engineered_mosquitoes_unintended_consequences.html; *see also* Claire Bernish, *Zika Outbreak Epicenter in Same Area Where GM Mosquitoes Were Released in 2015*, ANTI-MEDIA, http://theantimedia.org/zika-outbreak-epicenter-in-same-area-where-gm-mosquitoes-were-released-in-2015/ (last updated Feb. 4, 2016); Elle Griffiths, *Was Zika Outbreak Caused by Release of Genetically Modified Mosquitoes in Brazil?*, MIRROR, http://www.mirror.co.uk/news/world-news/zika-outbreak-caused-release-genetically-7281671 (last updated Feb. 2, 2016, 3:36 PM).

considering IE issues could be a national effort to consult the immediately next generation and report their concerns and hopes for gene drives back to policy makers.[51] Weiss names the current generation of children as "the first representatives of the future generations."[52] Consulting older youth about gene drives (e.g., those who can understand the technology, such as preteens or teens having taken some biology) and asking them their opinions could be an important starting point in improving IE of policy making. Applications of "next generation" biotechnologies such as gene drives present an area for which the input of the next generation is particularly important. The face of "nature" and human relationships with nature are shifting, yet those who are most likely to experience these changes, the young, are left out, and their voices are not heard by today's decision makers. We can at least provide opportunities for youth to discuss and report their hopes, concerns, and attitudes about next generation GE, including gene drives, while we encourage policy makers to adopt a longer term perspective for other future generations.

51. We have developed a project prospectus to do so at the Genetic Engineering and Society Center at North Carolina State University with several partners across the country.

52. E.B. Weiss, *In Fairness to Our Children: International Law and Intergenerational Equity*, 2 CHILDHOOD 22, 22 (1994).