ETHICAL CONSIDERATIONS FOR THE USE OF GENE DRIVES IN WILDLIFE

NOTE

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INTRODUCTION

Under the traditional Mendelian rules of inheritance, genes have a 50% chance of being passed on through sexual reproduction. However, there are certain naturally occurring selfish genetic elements known as "gene

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drives" that are biased in their chances of being inherited even if they reduce an organism's ability to reproduce.[1] While a wide variety of gene drives occur in nature and have been studied for the past fifty years, the 2012 development of clustered regularly interspaced short palindromic repeats ("CRISPR-Cas9" or "CRISPR") revolutionized the potential for humans to use gene drives to their advantage.[2]

CRISPR is a naturally occurring defense system that certain bacteria have developed to defend themselves against viruses, and scientists have modified this system to edit the genomes of nucleated organisms, including plants and animals.[3] When inserted into an organism, CRISPR can direct an enzyme, Cas9, to make specific cuts in the organism's genome, and this allows scientists to use a synthetic DNA sequence to repair the genome at this location.[4] More importantly, when CRISPR is used to cut specific sections of DNA in an organism's germ line and a gene drive is used to repair that cut, that gene drive can be copied and inherited by the organism's offspring and by all succeeding generations.[5]

The potential uses of CRISPR are wide-ranging, and they include applications in humans, crops, and wildlife species. In humans, the technology has already been tested to combat genetic diseases such as sickle cell anemia and an inherited form of blindness, though the use of CRISPR in humans has prompted public outcry because of its potential application in creating "designer babies."[6] The technology has also been used for COVID-19 testing, and a potential CRISPR-based COVID-19 vaccine has been studied as well.[7] In crops, research is underway to use CRISPR to make crops resistant to certain pathogens, to increase crop

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1 NAT'L ACADS. OF SCIS., ENG'G & MED., GENE DRIVES ON THE HORIZON: ADVANCING SCIENCE, NAVIGATING UNCERTAINTY, AND ALIGNING RESEARCH WITH PUBLIC VALUES 1-3 (2016) [hereinafter NAS, GENE DRIVES].

2 *Id.*

3 Irus Braverman, *Editing the Environment: Emerging Issues in Genetics and the Law*, *in* GENE EDITING, LAW, AND THE ENVIRONMENT: LIFE BEYOND THE HUMAN 1, 3-4 (Irus Braverman ed., 2018); *see also* NAS, GENE DRIVES, *supra* note 1.

4 Braverman, *supra* note 3, at 3.

5 *See id.* at 3-4; a "germ line" is "[a] cellular lineage in sexually reproducing organisms that produces the gametes (eggs and sperm) which transmit genetic material to the next generation." NAS, GENE DRIVES, *supra* note 1, at 1-3, 182.

6 *See, e.g.*, Karen Weintraub, *Despite Controversy, Human Studies of CRISPR Move Forward in the U.S.*, SCIENTIFIC AMERICAN, Aug. 13, 2019, https://www.scientificamerican.com/article/despite-controversy-human-studies-of-crispr-move-forward-in-the-u-s/; Kashyap Vyas, *Designer Babies: Gene-Editing and the Controversial Use of CRISPR*, INTERESTING ENGINEERING, July 4, 2019, https://interestingengineering.com/designer-babies-gene-editing-and-the-controversial-use-of-crispr.

7 Jennifer Straiton, *CRISPR vs COVID-19: How Can Gene Editing Help Beat a Virus?*, 69 BIOTECHNIQUES 327, 327 (2020); Timothy R. Abbott et al., *Development of CRISPR as a Prophylactic Strategy to Combat Novel Coronavirus and Influenza*, BIORXIV 1, 3, Mar. 14, 2020, https://www.biorxiv.org/content/10.1101/2020.03.13.991307v1.article-info.

yield, and to alter the nutrient content of certain foods.[8] The use of CRISPR in agriculture is particularly appealing because it can be used to alter a plant by deleting or reducing the expression of a gene without inserting foreign DNA, and thus these CRISPR-altered crops would not have the negative label of being genetically modified organisms, or "GMOs."[9] As for wildlife species, the potential applications of CRISPR include altering species to make them resistant to certain diseases (especially those that are transmitted to humans), suppressing populations of invasive species, adapting species threatened by stressors such as climate change, and even bringing extinct species back to life.[10]

While many of these applications of gene drives in wildlife are still hypothetical, some have been tested in labs. For example, CRISPR-based gene drives have been successfully inserted into yeast, fruit flies, and two species of mosquitoes.[11] In the fruit fly study, scientists successfully changed the color of female fruit flies from a darker body color to yellow. When these mutated females were mated with wild-type males, the gene drive was passed on to 97 percent of the female progeny.[12] In the first mosquito study in 2015, scientists drove two anti-parasite genes into a species of mosquito known to be a vector for malaria, and the results showed a 98.8 percent gene conversion rate in the third generation for both male and female progeny.[13] The following year, scientists inserted a gene drive designed to cause female sterility into another mosquito species, with a transmission rate of 91.4 percent to 99.6 percent observed in offspring.[14]

Other applications of gene drives in wildlife are still in the preliminary stage, though they are more controversial because they involve field trials. One of the most prominent examples is a study planned by Dr. Kevin Esvelt, an evolutionary engineer and assistant professor at the MIT Media Lab, who was credited as the first to describe how CRISPR could

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8 *See, e.g.*, Eric Niiler, *Why Gene Editing is the Next Food Revolution*, NAT'L GEOGRAPHIC, Aug. 10, 2018, https://www.nationalgeographic.com/environment/future-of-food/food-technology-gene-editing/.

9 *Id.*

10 NAS, GENE DRIVES, *supra* note 1, at 15-19.

11 Kevin Esvelt, *Rules for Sculpting Ecosystems: Gene Drives and Responsive Science*, *in* GENE EDITING, LAW, AND THE ENVIRONMENT: LIFE BEYOND THE HUMAN 21, 23 (Irus Braverman ed., 2018).

12 NAS, GENE DRIVES, *supra* note 1, at 33-34.

13 *Id.* at 34. A a gene conversion rate "describes how the gene drive is passed to subsequent generations when one parent carries the gene drive and the other does not." *Id.* at 3.

14 Hammond et al., A CRISPR-Cas9 *Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector Anopheles Gambiae*, 34 NAT. BIOTECH. 78 (2016).

be used to alter wildlife populations in an evolutionarily stable manner.[15] Esvelt founded the Mice Against Ticks project, which is described as "an experimental community-guided effort to prevent tick-borne disease by altering the shared environment."[16] The project intends to use CRISPR to make white-footed mice immune to Lyme disease, as these mice are important reservoirs for infecting ticks with the pathogen.[17] Field trials were proposed for the island communities of Nantucket and Martha's Vineyard in Massachusetts, though community engagement efforts created skepticism and worries over the potential consequences, even prompting a documentary series about the heated town hall meetings where the trials were deliberated.[18]

The community concerns associated with gene drives parallel worries generated by other genetic experiments. For example, one proposed field study involves the release of sterile male mosquitoes in the Florida Keys by the British biotechnology company Oxitec, though Oxitec is currently using a genetic engineering technique that does not involve gene drives. Oxitec has already conducted field trials with these genetically modified mosquitoes in Brazil, the Cayman Islands, Panama, and Malaysia, leading to a 90 percent decrease in local mosquito populations.[19] The company proposed a field trial in the Florida Keys in order to control the spread of the Zika virus, though a referendum held in 2016 showed split results: Monroe County as a whole (the county covering the Florida Keys) voted 58 to 42 percent in favor of the field trial, while the community of Key Haven (where the trial would be held) opposed the project by a 65-35 margin.[20] Though the mosquitos will phase out of wild populations through natural selection if edited mosquitoes are not routinely released, community concerns remain.[21]

As the projects in Massachusetts and Florida show, the use of CRISPR-based gene drives in wildlife is contested, as it is a new, unfamiliar technology that has the potential to radically change the relationship that

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15 Biography of Dr. Kevin Esvelt, MIT MEDIA LAB, https://www.media.mit.edu/people/esvelt/overview/ (last visited Apr. 5, 2020).

16 Joanna Buchthal et al., *Mice Against Ticks: An Experimental Community-Guided Effort to Prevent Tick-Borne Disease by Altering the Shared Environment*, 374 PHIL. TRANSACTIONS R. SOC. B. 1 (2018).

17 *Id.* at 3.

18 UNNATURAL SELECTION (Netflix 2019); *see also* Buchthal et al., *supra* note 16, at 6-7.

19 Irus Braverman, *Gene Drives, Nature, Governance: An Ethnographic Perspective*, *in* GENE EDITING, LAW, AND THE ENVIRONMENT: LIFE BEYOND THE HUMAN 55, 65-66 (Irus Braverman ed., 2018).

20 *Id.*

21 *See* JENNIFER A. DOUDNA & SAMUEL H. STERNBERG, A CRACK IN CREATION: GENE EDITING AND THE UNTHINKABLE POWER TO CONTROL EVOLUTION 150 (2017) (noting how Oxitec's technology is limited by natural selection).

humans have with nature. The technology also comes with myriad risks, including passing the gene drive to a non-target species and dangerous interactions between the gene drive and other genes in an organism.[22] This Note is limited to a discussion of the uses of these gene drives in wildlife species and the main ethical issues associated with these uses, and it argues that, even with these concerns, further research and progress in this area is warranted. Moreover, any analysis of gene drives in this Note refers to the genetic engineering use of gene drives (through CRISPR-based technologies), rather than the study of naturally occurring gene drives. Part I addresses how the use of wildlife-editing gene drives may prompt necessary changes in how humans interact with and view the natural world. In addition to provoking a discussion about how humans value nature, humans are currently living in the Anthropocene epoch—the "age of humans."[23] Wildlife gene drives are an important example of how, in the Anthropocene, humans must come to terms with the reality that human intervention is needed to some extent in order to safeguard "nature."

Part II then discusses the risk analysis issues that must be addressed and overcome in order to successfully deploy gene drives in wildlife, including problems involving the anti-science movement, ecological risk assessment, and intergenerational equity. Part III concludes with a plea for effective public engagement in implementing gene drives in wildlife, noting the unique position of the "scientist-regulator hybrid," and his or her duty to bring procedural justice to affected communities.

I. GENE DRIVES REPRESENT A NECESSARY CHANGE IN HUMANS' RELATIONSHIP WITH NATURE

Dr. Jennifer Doudna, a biochemist at the University of California, Berkley, pioneered CRISPR in 2012, an effort now credited as "one of the most monumental discoveries in biology."[24] A couple of years later, Doudna wrote a book explaining the discovery, and she had the following to say about the ecological consequences of the technology:

> Humans have been changing the genetic makeup of plants and animals since long before the advent of genetic engineering. Should we refrain from influencing our environment with this

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22 NAS, GENE DRIVES, *supra* note 1, at 112.

23 Noel Castree, *An Official Welcome to the Anthropocene Epoch – But Who Gets to Decide It's Here?*, THE CONVERSATION, Aug. 30, 2016, https://theconversation.com/an-official-welcome-to-the-anthropocene-epoch-but-who-gets-to-decide-its-here-57113.

24 Andrew Pollack, *Jennifer Doudna, A Pioneer Who Helped Simplify Genome Editing*, N.Y. TIMES, May 11, 2015, https://www.nytimes.com/2015/05/12/science/jennifer-doudna-crispr-cas9-genetic-engineering.html.

> new tool even though we haven't showed such restraint in the past? Compared to what we've done to our planet already, whether intentional or not, is CRISPR-based gene editing any less natural or any more harmful? There are no easy answers to these questions.[25]

After making this comment, Doudna went on to say that even more difficult questions arise when CRISPR is combined with gene drives to be used in wildlife species, since this combination may have consequences more powerful than any changes humans have made to the natural world so far. CRISPR-based gene drives, as Doudna explained, would allow humans to "outsmart natural selection" in certain species indefinitely and at unprecedented speeds.[26] This is all a matter of perspective, however. It is true that CRISPR-based gene drives can alter wildlife species at the biological level in novel ways, but it is difficult to compare these alterations on a systemic level to the ecological alterations that humans have already imposed on the planet. Instead of focusing on this comparison between biology and ecology, I argue that wildlife gene drives represent a way to find value in both nature and in human invention, as well as a necessary expansion of what humans view as "natural" in the Anthropocene.

A. Wildlife Gene Drives: Finding Value in Both Nature and in Human Invention

Discussions about what it means to "value" nature can easily devolve into esoteric debates between the anthropocentric, ecocentric, and biocentric worldviews. On the one hand, it can be argued that nature has intrinsic value that must be considered in decisions that involve its alteration, while others contend that nature only has value in relation to human use—a utilitarian point of view.[27] At the outset, it must be conceded that the potential use of gene drives in wildlife is largely a utilitarian endeavor, especially if these gene drives are used to eradicate vector-based diseases such as malaria and Lyme disease. The use of gene drives to suppress invasive species or to bring extinct species back to life can also be thought of as a utilitarian process, since it requires humans to decide they value the invasive species little enough to eradicate it, or value an extinct species greatly enough to revive it. Moreover, if nature was thought to have intrinsic value, it would be difficult to justify a

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25 DOUDNA & STERNBERG, *supra* note 21, at 147-48.

26 *Id.* at 150-51.

27 For a discussion of the conflict among these three worldviews, *see, e.g.*, BENJAMIN FRANKS ET AL., ENVIRONMENTAL ETHICS AND BEHAVIOURAL CHANGE 48-74 (2018).

decision to alter something so essential to a species' existence as its genes.[28]

This is not to say that the use of gene drives in wildlife should bend unreservedly to an anthropocentric, utilitarian worldview; there must be limits on gene drive applications so that the technology is not used "for the sole purpose of satisfying idiosyncratic aesthetic preferences of humans."[29] These limits would not be imposed on a bright-line basis, and therefore they do not necessarily require one to believe that nature has intrinsic value that cannot be undermined. However, the limits to gene drives do show some appreciation for the laws of the natural world, and thus the application of gene drives in wildlife may be categorized as a pluralistic approach.[30] For example, eradication of certain species using gene drives could be limited to those species deemed "invasive" (a subjective term);[31] this limit shows at least a modest appreciation for nature because the goal is to stabilize ecosystems. On the contrary, using gene drives to make an animal bioluminescent or to bring back to life a species that became extinct without human intervention (e.g., the wooly mammoth)[32] involves little to no appreciation for nature in itself and should likely not be permissible. Even if nature is only valued for its association with humans, that does not mean that nature can be totally ignored in future applications of gene drives.

Aside from showing that the value of nature is a malleable concept, wildlife gene editing is important because it teaches humans to find value in both nature and human invention. In 2016, the National Academy of Sciences ("NAS") published a report regarding the state of the science and future expectations for gene drives. The report summarized the philosophical tension as follows:

> The two kinds of value [ ] contrast with each other to some degree; finding value in nature seems to call for adjusting human activity in order to accommodate nature, while finding value in knowledge, understanding, invention, innovation, and industry

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28 For an argument for considering the intrinsic value of nature, *see, e.g.*, LEENA VILKKA, THE INTRINSIC VALUE OF NATURE (Robert Ginsberg ed., 1997).

29 DOUDNA & STERNBERG, *supra* note 21, at 143 (quoting bioethicist Jeantine Lunshof).

30 Pluralism is a stance that allows for the appreciation of multiple ethical philosophies, and it may be used to reconcile anthropocentric, ecocentric, and biocentric approaches. *See, e.g.*, Peter S. Wenz, *Minimal, Moderate, and Extreme Pluralism*, *in* LAND, VALUE, COMMUNITY: CALLICOTT AND ENVIRONMENTAL PHILOSOPHY 185-96 (Wayne Ouderkirk & Jim Hill, eds. 2002).

31 *See* Robert I. Colautti & Hugh J. MacIsaac, *A Neutral Terminology to Define 'Invasive' Species*, 10 DIVERSITY & DISTRIBUTIONS 135 (2004) (discussing the subjective use of the term "invasive species").

32 *See* NAT'L ACADS. OF SCIS., ENG'G & MED., PREPARING FOR FUTURE PRODUCTS OF BIOTECHNOLOGY 47, 49 (2017) (discussing how technology such as CRISPR is being researched for these applications).

> seems to celebrate the alteration of nature to support human activity. On the other hand, it may be possible . . . to share both values to some extent. Perhaps, each stance even implicates the other: Preservation of natural phenomena can be aided by appropriately directed efforts to understand and intervene in the world, and human activity in the world depends on trying to accommodate the natural world.[33]

As this quote suggests, the default assumption is that the value people find in nature and in human invention seem, at first glance, to be in direct opposition to each other. This is an example of apparent value conflict, where the traditional approach would be to conduct a tradeoff analysis to decide whether or not to use gene drives in wildlife species.[34] This type of analysis would use terms like "balance" and "cost-benefit," and it assumes that the competing values are commensurable (i.e., they can be recast as contributing to a single norm).[35] However, public policy scholars, including Professors David Thacher and Martin Rein, have criticized this approach because it is too algorithmic and it incorrectly assumes that policy makers treat conflicting values as commensurable. Rather, these scholars argue that policy makers deal with value conflict in different, case-specific ways.[36]

In the context of wildlife gene drives, the value conflict can be solved by understanding that the value people find in nature and in human invention are in symbiosis with each other. The organization found in nature (e.g., DNA) is what makes human invention possible, and it also sets the limits of human invention. For instance, gene drives work best in species that reproduce sexually and have short generation timelines.[37] These are important boundaries that nature has imposed on this technology.[38] Moreover, scientists can impose boundaries on the use of wildlife gene drives to ensure that they do not propagate indefinitely, as evidenced by research into "daisy drives," specially designed gene drives that can override and revert CRISPR-facilitated genetic changes.[39] As the

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33 NAS, GENE DRIVES, *supra* note 1, at 74-75.

34 *See* David Thacher & Martin Rein, *Managing Value Conflict in Public Policy*, 17 GOVERNANCE 457, 462 (2004).

35 *Id.* at 457-58.

36 *Id.* (maintaining that "rationality is often less algorithmic than traditional views have suggested, in that it relies on situated judgements about what is appropriate in particular times, places, and contexts . . . ").

37 *See* NAS, GENE DRIVES, *supra* note 1, at 50.

38 However, while the requirement of sexual reproduction has been assumed, recent research has shown that gene drives can possibly be used in other organisms, such as viruses. *See* Marius Walter & Eric Verdin, *Viral Gene Drive in Herpesviruses*, 11 NATURE COMM. 1 (2020).

39 *See* Esvelt, *supra* note 11, at 31-32 (discussing the development and promise of the daisy drive technology).

NAS report suggests, the value people find in nature and in human invention can and do implicate each other in the context of gene drives.

B. The Necessary Role of Wildlife Gene Drives in the Anthropocene Epoch

An epoch is a unit of geologic time characterized by a series of rock layers deposited on the Earth; transitions between epochs are often associated with dramatic climate events such as ice ages.[40] While the current Holocene epoch started with the end of the last ice age, some scientists have begun to argue that the Earth has now entered the Anthropocene epoch—the "age of humans."[41] The exact date of this change is debatable, but one proposed year is 1950, since that is when humans began making permanent stratigraphic impacts on Earth through, among other things, greenhouse gas emissions, nuclear bomb testing, disposable plastics, and fertilizer.[42] Whether or not one believes these events warrant a new epoch, it is undeniable that humans have impacted Earth to such an extent that a new way of understanding the relationship our species has with the planet is required.

The competing ethical stances of biocentrism, ecocentrism, and anthropocentrism have different ideas of what humans should do with regards to nature in the Anthropocene.[43] When it comes to the use of gene drives in wildlife species, it is possible to hypothesize what each ethical camp would do: biocentrists would refuse to use gene drives at all because it interrupts the inherent value of individual organisms, ecocentrists may allow it in some circumstances where it is used to promote ecological stability but would likely not allow it for purposes such as human health, and anthropocentrists would allow its use in a more or less unrestricted way.[44] While this Note does acknowledge that the use of wildlife gene drives has an anthropocentric underpinning, the NAS report summarized what should be done: "[p]assing this boundary [into the Anthropocene] is seen sometimes as evidence of the need for greater restraint towards nature, and sometimes as showing that humans should

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40 *See, e.g.*, Eric Biber, *Law in the Anthropocene Epoch*, 106 GEO. L. J. 1, 3 (2017).

41 Noel Castree, *An Official Welcome to the Anthropocene Epoch – But Who Gets to Decide It's Here?*, THE CONVERSATION, Aug. 30, 2016, https://theconversation.com/an-official-welcome-to-the-anthropocene-epoch-but-who-gets-to-decide-its-here-57113.

42 *Id.*

43 *See, e.g.*, NAS, GENE DRIVES, *supra* note 1, at 73-75 (noting the tension between these ethical stances when applied to gene drive use).

44 These are general, overly simplistic assumptions, though they are helpful for understanding the disagreement between the three ethical stances. *See id.*

accept a strongly interventionist role in nature, for they are in that role whether they like it or not."[45]

The duties humans have toward the natural world during the Anthropocene are contextual, and it may be helpful to think of these duties as encompassing something like a "gardening" ethic that values the alteration and accommodation of nature simultaneously.[46] The idea behind the gardening ethic is that humans have altered nature to the point where it has become like a garden where humans have a responsibility to tend to nature and make sure it does not implode under the stresses that they have imposed upon it.[47] In some instances, this duty will involve human intervention, but in others it will involve the opposite.[48]

Of course, some people may see this argument for a gardening ethic and "decry the 'end of nature' and the loss of the sense of a reality outside ourselves."[49] However, even though it may sound bleak, humans now live in a world where no part of "nature" has been left untouched by humans. For example, perfluorooctanoic acid, a non-degradable chemical used to make Teflon, now contaminates virtually all ecosystems on Earth and is present in the blood of 99% of Americans.[50] Moreover, the only places thought to have no non-native species brought in by humans are isolated, uninhabitable ecosystems, such as deserts, caves, and deep sea geothermal vents.[51]

Nonetheless, reframing nature as a garden comes with an expanded notion of what it means to conserve nature. In the traditional sense, conservation involves action at the ecological level, but with technologies such as gene drives, humans have the ability conserve via action at the biological level.[52] Given what humans have already put this planet through, it may be unethical in certain situations to not at least consider

45 *Id.* at 75.

46 *See id.*; *see also* EMMA MARRIS, THE RAMBUNCTIOUS GARDEN: SAVING NATURE IN A POST-WILD WORLD (2011).

47 *See generally* Marris, *supra* note 46.

48 Ronald Sandler, *Gene Drives and Species Conservation: An Ethical Analysis*, *in* GENE EDITING, LAW, AND THE ENVIRONMENT: LIFE BEYOND THE HUMAN 39, 41-43 (Irus Braverman ed., 2018) ("[A] blanket position [to intervention in the Anthropocene epoch] is not likely to be justified.").

49 R. Alta Charo & Henry T. Greely, *CRISPR Critters and CRISPR Cracks*, 15 AM. J. BIOETHICS 11, 15 (2015).

50 *See, e.g.*, Kellyn S. Betts, *Perfluoroalkyl Acids: What the Evidence is Telling Us*, 115 ENVTL. HEALTH PERSP. 250 (2007); Johnna Crider, *Toxic Chemical in 99% of Americans' Blood*, CLEANTECHNICA, Oct. 19, 2019, https://cleantechnica.com/2019/10/19/toxic-chemical-in-99-of-americans-blood/.

51 Rachel Nuwer, *The Last Places on Earth with No Invasive Species*, BBC, Sept. 8, 2014, https://www.bbc.com/future/article/20140909-are-alien-species-everywhere.

52 *See generally* Sandler, *supra* note 48.

the use of wildlife gene drives as a conservation tool.[53] For example, the need for the Mice Against Ticks project was created by the increased prevalence of Lyme disease, which was driven by human action: humans caused forest fragmentation and an associated increase in the forest edge habitat in which white-footed mice thrive.[54] To not consider the use of wildlife gene drives to solve the problem could amount to a form of ecological insensitivity, especially if the alternatives are more damaging or less effective.

II. Risk Analysis Concerns with Wildlife Gene Drives

Apart from the value-laden problems surrounding the use of gene drives in wildlife, one of the most important ethical issues in this area of scientific study involves risk. Some critical risk-related questions include how persistent a gene drive will be between generations, whether there is a chance that the gene drive could pass to a non-target species, how the gene drive could interact with other genes in the edited organism, and whether there are viable mitigation strategies to undo the effects of a gene drive if needed.[55] Ethical considerations help assess how these risks are valued and judged against one another, and ethics ultimately informs the guidelines for appropriate actions given these risks.[56]

Three risk-related issues involving wildlife gene drives implicate ethical responses. First, the growing anti-science movement has and will continue to plague progress in gene drive research by prompting public alarmism, and researchers have a responsibility to combat this problem by being transparent with their work, along with using community engagement tactics as discussed in Part III. Second, there needs to be an honest discussion of whether ecological risk assessment is the appropriate tool to structure decisionmaking with respect to gene drives in wildlife, given that many of the relevant risks are cultural and difficult to quantify. Lastly, because these gene drives may impact species permanently, intergenerational equity considerations are a necessary component of any subsequent risk analysis.

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53 *See* Esvelt, *supra* note 11, at 26 ("In the context of the Anthropocene and the sixth great mass extinction, gene drives are small potatoes, especially because phenotypic changes can be overwritten.") (internal citations omitted).

54 *See* Buchthal et al., *supra* note 16.

55 NAS, Gene Drives, *supra* note 1, at 117-18.

56 *See, e.g.*, *Why Link Risk Management and Ethics?*, Int'l Risk Mgmt. Inst., https://www.irmi.com/articles/expert-commentary/why-link-risk-management-and-ethics (last visited Apr. 5, 2020).

A. Combatting the Anti-Science Movement with Transparency

Historically, the public put a blind trust in scientists because the scientific discipline was thought of as an objective enterprise. As the public has come to realize that scientists can be influenced by mixed motives, that trust has understandably eroded, and this erosion has warped the public's perception of risk. "Public alarmism is the public response to new scientific techniques that challenge traditional norms," especially in the area of genetic engineering where the ethical lapses of companies like Monsanto have clouded any progress in widespread public suspicion.[57] Moreover, it does not help that the U.S. military is the largest global investor in gene drive research, since this generates even more alarm over the potential for gene drives to be used as weapons.[58]

Some believe that the anti-science movement, along with the secrecy of current patent and scientific publication processes, contributes to the closed-door policy of genomic research. In turn, this closed-door policy creates and environment where the public has little understanding of key information.[59] Esvelt gives an example of how public perception could have a devastating impact on the future use of wildlife gene drives. He hypothesizes a field trial where the edited organisms escape the trial area and mate with wild populations, eventually spreading the drive to every population of that species in the world:

> Imagine the headline: "Scientists accidentally convert an entire wild species to GMOs. Is CRISPR to blame?" The damage to public trust in scientists and governance would be severe and long lasting. At a minimum, it would be the end of hopes to use gene drives against malaria and schistosomiasis. A mere decade-long delay could keep us from preventing millions of deaths and billions of infections.[60]

This shows why scientists have a responsibility to conduct their gene drive research transparently: if the public is left ill-informed, public alarmism could take over and prevent these scientists from saving both human lives and ecosystems. To combat this secrecy and facilitate the

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57 Sadie Grunewald, *CRISPR's Creatures: Protecting Wildlife in the Age of Genomic Editing*, 37 UCLA ENVTL. L. & POL'Y 1, 21-22 (2019); *see also* Esvelt, *supra* note 11, at 26. Monsanto, a former agricultural company, was heavily criticized for inappropriately influencing the scientific research that reviewed the company's herbicides and GMO crops. *See, e.g.*, *What the Monsanto Papers Tell Us About Corporate Science*, CORP. EURO. OBSERVATORY (Jan. 3, 2018), https://corporateeurope.org/en/food-and-agriculture/2018/03/what-monsanto-papers-tell-us-about-corporate-science; *Do Seed Companies Control GM Crop Research?*, SCIENTIFIC AM, Aug. 1 ,2009, https://www.scientificamerican.com/article/do-seed-companies-control-gm-crop-research/.

58 *See* Grunewald, *supra* note 57, at 21.

59 *See id.* at 17.

60 Esvelt, *supra* note 11, at 26.

responsibility researchers have to go forward with gene drive research, transparency is needed to inform the public of the real risks.[61] This involves, for example, raising awareness of safeguards that can prevent accidental releases of gene drives, as well as developing technology that can reverse certain negative consequences (e.g., daisy drives).[62]

As Esvelt contends, "[r]aising awareness is all the more essential because existing biosafety committees and authorities are simply not qualified to evaluate gene drive risks."[63] This lack of regulation underscores the importance of scientists' "social license" to research wildlife gene drives. The concept of a social license explains how, even if a researcher fulfills all legal requirements for his or her research, positive public perception is still necessary in order to go forward.[64] While public education may not be enough to calm all fears concerning gene drives, it is certainly a step in the right direction and an important component of any risk analysis in this line of research.

B. Evaluating the Role of Ecological Risk Assessment in the Use of Wildlife Gene Drives

Ecological risk assessment is "the study and use of probabilistic decisionmaking tools to evaluate the likely benefits and potential harms of a proposed activity on the wellbeing of humans and the environment, often under conditions of uncertainty."[65] It is prized as a flexible approach that can be used to analyze scientific information in light of social, legal, political, and economic factors. The NAS report suggests that this framework is suitable to evaluate the risks associated with gene drive-modified organisms.[66] It is also the preferred risk assessment process used by governmental entities such as the U.S. Environmental Protection Agency ("EPA") and the European Environment Agency.[67]

In ecological risk assessment, the term "risk" encompasses four elements: probability (to evaluate the occurrence of ecological stressors), cultural values (to select endpoints, or project goals), public engagement (to incorporate cultural values), and uncertainty (to account for variability in environmental systems, knowledge base, and cultural values and social

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61 Esvelt, *supra* note 10, at 25-27 (noting that gene drive risks are primarily social in scope).
62 *Id.* at 31-32.
63 *Id.* at 26.
64 *See, generally, e.g.*, P. Carter et al., *The Social License for Research: Why Care.data Ran into Trouble*, 5 J. MED. ETHICS 404 (2015).
65 NAS, GENE DRIVES, *supra* note 1, at 112.
66 *Id.* at 118.
67 *See* U.S. EPA, GUIDELINES FOR ECOLOGICAL RISK ASSESSMENT (1998); EUROPEAN ENVT. AGENCY, ENVIRONMENTAL RISK ASSESSMENT: APPROACHES, EXPERIENCES, AND INFORMATION SOURCES (2008).

norms).[68] Moreover, ecological risk assessment is performed in three phases: problem formation (an information-gathering phase), analysis (to characterize both effects and exposure to a stressor), and risk characterization (where the results of the previous stage are used to estimate risk).[69] While ecological risk assessment provides an organized structure that is certainly relevant to assessing the risk of using gene drives in wildlife species, the framework has certain pitfalls that must be addressed before it is used.

For one, ecological risk assessment assumes agreement about the cultural values used in selecting an endpoint. This agreement typically takes the form of laws and regulations that embed certain cultural values—for example, the Endangered Species Act harbors a strong preference for wildlife conservation, even if the economic costs of such conservation are exorbitant.[70] For the use of gene drives in wildlife, however, there are no laws (in the U.S., at least) that adequately capture cultural values on the subject. As discussed in Part I, this area of scientific research will force humans to intertwine the value found in nature and in human invention. Until that has occurred, it will be difficult for an ecological risk assessment to get past the problem-formation stage. Moreover, since some applications of wildlife gene drives will be used to eradicate human diseases, the use of ecological risk assessment may butt heads with other public health-based risk assessment programs.[71]

Another problem with ecological risk assessment is that it boils down normative values into quantitative, probabilistic outcomes, and it also involves terms that may seem objective but which are actually value-laden. While the NAS report explains that "[g]iven adequate criteria, it is possible to express cultural values mathematically in the definition of endpoints,"[72] an issue with wildlife gene drives is that the endpoints may not be representative of any concrete cultural values. For instance, philosophical scholar Dr. Kristin Shrader-Frachette has explained that a common endpoint in ecological risk assessment is "ecological health."[73] This term, however, is too vague and all-encompassing to be helpful—it "involves the welfare of different species, functions, and systems, not all

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[68] See NAS, GENE DRIVES, *supra* note 1, at 113.

[69] *Id.* at 116; *see generally* U.S. EPA, *supra* note 67.

[70] NAS, GENE DRIVES, *supra* note 1, at 113; *see also* Endangered Species Act, 16 U.S.C. § 1531 *et seq.* (2012).

[71] For example, the EPA has its own framework for human health risk assessment. *See Human Health Risk Assessment*, EPA, https://www.epa.gov/risk/human-health-risk-assessment (last visited Apr. 5, 2020).

[72] NAS, GENE DRIVES, *supra* note 1, at 113.

[73] Kristin Shrader-Frechette, *Ecological Risk Assessment and Ecosystem Health: Fallacies and Solutions*, 3 ECOSYSTEM HEALTH 73, 74-75 (1997).

of which can be maximized at once," and "ecologists rarely have extensive, general, inductive knowledge of ecosystem health."[74] The NAS report makes a similar argument: "an ecosystem's 'health' is a normative claim regarding a characteristic (health) that is not an inherent property of the system, but rather the meaning draws on an often unspecified value system."[75]

Using vague terms like "ecosystem health" in an ecological risk assessment contributes to a level of linguistic uncertainty that may allow certain parties to take advantage of the system.[76] If a risk assessment is viewed as a social construct where the methods used are highly malleable, Schrader-Frechette argues that "those with money, power, and influence (usually industry and developers) control risk assessment and bend the risk 'constructs' to serve their own ends and purposes."[77] This can be highly problematic for the future of wildlife gene drives, especially since genetic engineering is already clouded in suspicion because of previous mishaps. In order to ward against this, any ecological risk assessment in this area should use terms that are more concrete and quantifiable, such as species richness, species diversity, and species evenness.[78]

C. Intergenerational Equity Considerations

The concept of intergenerational equity derives from "the perspective of a generation which is placed somewhere on the spectrum of time, but does not know in advance where."[79] It involves fairness in how the conditions of the natural world are left for succeeding generations, and it can sometimes be quantified via discount rates for risks in environmental decisionmaking, especially in the context of climate change issues.[80] International environmental law scholar Edith Brown Weiss has formulated three principles of intergenerational equity: conservation of options (i.e., conserving diversity of natural resources), conservation of quality ("leaving the planet no worse off than received"), and

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74 *Id.* at 75.

75 NAS, GENE DRIVES, *supra* note 1, at 117.

76 *See id.* at 116-17.

77 Schrader-Frechette, *supra* note 73, at 77.

78 *See id.* at 76; Mark Pyron, *Characterizing Communities*, 3 NATURE EDU. KNOWLEDGE 39 (2010) ("Species richness is simply the number of species in a community. Species diversity is more complex, and includes a measure of the number of species in a community, and a measure of the abundance of each species. Species diversity is usually described by an index, such as Shannon's Index H'. Species evenness is a description of the distribution of abundance across the species in a community.").

79 Edith Brown Weiss, *Climate Change, Intergenerational Equity, and International Law*, 9 VT. J. ENVTL. L. 615, 622 (2008).

80 *See, e.g.*, Julian Roche, *Intergenerational Equity and Social Discount Rates: What Have We Learned Over Recent Decades?*, 43 INT'L J. SOC. ECON. 1539 (2015).

conservation of access ("equitable access to the use and benefits of the legacy of past generations").[81] Along with these principles come five duties of use: the duties to conserve resources, ensure equitable use, avoid adverse impacts, prevent disasters (and to minimize damage and provide emergency assistance), and compensate for environmental harm.[82]

Given that wildlife gene drives have the potential to be permanent and will most definitely affect succeeding generations, any meaningful risk analysis in this area of study must involve intergenerational equity considerations. This process would be contextual, especially since the different applications of these gene drives will impact future generations in different ways. For instance, the use of gene drives to suppress invasive species populations may be favorable from an intergenerational equity standpoint.[83] If the gene drive is kept local (e.g., on an island, as in the Mice Against Ticks project), it would preserve Weiss's conservation of access principle since the invasive species would not be totally eradicated from the world, and the populations left would not have edited genes.[84] However, such a project may violate intergenerational equity considerations from a cultural standpoint. For example, feral pigs are invasive in Hawaii, but eradication may be unjust since local cultures have come to rely on these pigs for ceremonial use.[85]

A different prominent application of gene drives in wildlife—to eradicate human diseases by blocking vector species from carrying these diseases—would involve different intergenerational equity considerations. The chief concerns with this application would be that future generations would no longer be able to enjoy a purely "wild" species, and that the gene-edited species would have negative ecological effects (e.g., by disrupting the food chain).[86] Using Weiss's terminology, using gene drives to eradicate vector-borne diseases could violate the principle of conservation of quality and the duty to prevent adverse impacts.[87] Moreover, these violations would need to be weighed against the human health benefits that these gene drives could give future generations, along with the right the current generation has to use the natural world for self-preservation.[88]

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81 Weiss, *supra* note 73, at 616.

82 *See* Jennifer Kuzma & Lindsey Rawls, *Engineering the Wild: Gene Drives and Intergenerational Equity*, 56 JURIMETRICS 279, 282 (2016) (listing the duties formulated by Weiss).

83 *Id.* at 291-92.

84 *See, e.g., id.*

85 *See id.*

86 *See id.* at 287-90.

87 *Id.*

88 *Id.* at 288.

III. PUBLIC ENGAGEMENT AS KEY TO THE SUCCESSFUL USE OF GENE DRIVES IN WILDLIFE

In Esvelt's Mice Against Ticks project, the choice to use Martha's Vineyard and Nantucket as locations for potential field trials was not random. While small islands are preferable for gene drive trials because the edited wildlife populations have a lesser chance of spreading across the mainland, this was not Esvelt's only consideration.[89] Namely, Martha's Vineyard and Nantucket represented suitable locations from a community engagement perspective. The residents of these islands generally have a high average level of education, suggesting that the islands' populations would be well-suited to guiding research.[90] Moreover, these communities have long traditions of New England-style town hall democracy. Esvelt was able to capitalize on this by holding numerous town hall meetings where he explained his research, residents voiced their concerns, and both sides made suggestions to alter the project.[91] One important change prompted by the community, for example, was to use the description "engineered by shuffling native mouse-resistant DNA" instead of the misleading term "engineered, but 100% mouse."[92]

The Mice Against Ticks project shows the importance of crafting an effective community engagement process for wildlife gene drive research. Precisely because such research involves important value choices that may differ between communities, community engagement is critical in order for scientists to implement gene drive research with the requisite social license. The regulation of gene drive research is in a nascent stage, and therefore scientists in this arena have a duty to engage communities as a part of their role as a "scientist-regulator hybrid." Moreover, there are important ethical questions that must be addressed and overcome through community engagement, including which communities should be engaged and how their consent to this research should be obtained.

A. The Duty of the Scientist-Regulator Hybrid to Engage Affected Communities

It is unclear how wildlife gene drives will be regulated, especially in the United States. It is generally agreed upon that field experiments of these gene drives will fall under the regulatory umbrella of the

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89 Buchthal et al., *supra* note 16, at 6.
90 *Id.*
91 *Id.*
92 *Id.* at 7.

Coordinated Framework for the Regulation of Biotechnology ("Coordinated Framework"), a framework that allocates the regulation of biotechnology products under existing federal statutes administered by the EPA, U.S. Food and Drug Administration ("FDA"), and the U.S. Department of Agriculture ("USDA").[93] Which agency regulates a certain product depends on the product's intended use, such as for food (USDA) or disease control (FDA), and since wildlife gene drives have a number of different applications, regulatory jurisdiction would need to be decided on a case-by-case basis.[94]

Because wildlife gene drives would be released into the natural environment with potential for wide-ranging consequences beyond the intended goal, it is unclear if these gene drives could (or should) be categorized neatly into one of these three agencies' regulatory domains. For example, as explained in the NAS report, the FDA asserted regulatory authority over Oxitec's genetically engineered mosquito as a "new animal drug," though it is unclear how that authority was determined via the Coordinated Framework and associated guidance documents.[95] The regulation of gene drive-modified mice could fall under the domain of any of the three agencies, depending on if mice are viewed as a plant pest (USDA), if the gene drive is considered to be a new animal drug (FDA), or if the process is labeled as a form of pesticide/rodenticide (EPA).[96] Even if the three agencies were able to coordinate and have overlapping authority for a gene drive project, each agency has different methods for assessing risk and including public input, and this can result in a bureaucratic mess.[97]

This regulatory uncertainty means that scientists have a role to fill in the process that goes beyond their traditional occupational duties. "[T]he implementation of social responsibility in the United States has been left virtually solely to scientists," and "[i]t is in this regulatory void that the operating scientist becomes a self-regulator, her values and visions that much more important as they at least partly determine the scope of the research that she will undertake and its normative dimensions."[98]

One important duty an agency has in making regulatory decisions is to ensure due process by eliciting input from affected stakeholders. This occurs, for example, under the notice-and-comment rulemaking

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93 *See* Carlene Dooley, *Regulatory Silos: Assessing the United States' regulation of Biotechnology in the Age of Gene Drives*, 30 GEO. INT'L ENVTL. L. REV. 547, 556-60 (2018).

94 *Id.* at 556.

95 NAS, GENE DRIVES, *supra* note 1, at 155.

96 *Id.*

97 *See id.* at 158 (noting the confusion over regulatory jurisdiction for Oxitec's project).

98 Braverman, *supra* note 3, at 56.

proceedings required under the Administrative Procedure Act, and it also comes into play with the "reasonable public notice" requirement for environmental assessments mandated under the National Environmental Policy Act.[99] But for scientists conducting research on wildlife gene drives, government-mandated public engagement is uncertain. Scientists must recognize this and pick up the slack if they wish to preserve their social license. This duty of the scientist-regulator hybrid has been characterized by Esvelt as follows:

> [S]cientists have an obligation to openly share their plans, invite suggestions and concerns, disclose experimental results as soon as possible, and redesign the technology as needed. Applied to gene drives, such an approach will also have a greater chance of earning popular support for applications that could save millions of lives and rescue numerous species from extinction.[100]

B. Ethical Questions That Must Be Addressed in Community Engagement Efforts

The duty of the scientist-regulator hybrid holds little value if it does not involve specific responsibilities required to fulfill the duty. At its core, any community engagement effort has the goal of obtaining consent from the affected community, but in many situations, including in wildlife gene drive projects, it is difficult to ascertain what the relevant "community" is. The NAS report poses the following difficult questions on this subject:

> What groups have sufficient "stake" to be considered stakeholders? Must they be impacted directly? Must they already be involved in the problem? Must they have financial stake? Do stakeholders change with the phase of gene drive development and deployment? Do gene-drive modified organisms that are meant to spread geographically implicate even more numerous communities?[101]

These questions show that the identity of the affected "community" can change over time and space, and it likely cannot be defined adequately through existing mechanisms, such as through the requirements of legal standing.[102] Moreover, important racial and socioeconomic considerations must be taken into account in order to

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99 *See* Administrative Procedures Act, 5 U.S.C. § 500 *et seq.* (2012); National Environmental Policy Act, 42 U.S.C. § 4321 *et seq.*

100 Braverman, *supra* note 3, at 63 (quoting Dr. Kevin Esvelt).

101 NAS, GENE DRIVES, *supra* note 1, at 137.

102 For the requirements and limits on standing, *see, e.g.*, Massachusetts v. EPA, 549 U.S. 497 (2007).

equitably involve an affected community. In the Mice Against Ticks project, for example, Esvelt selected Martha's Vineyard and Nantucket partly because those communities are well-educated, but this judgement contains the potential discriminatory reasoning that less educated communities are not capable of understanding and contributing to this valuable research.[103] Similar concerns will govern engagement for wildlife gene drive projects in developing countries aimed at combatting vector-borne diseases such as malaria.[104]

After identifying the relevant community for an engagement effort, scientists must still grapple with what exactly it means to obtain "consent" from this community. The process for obtaining consent cannot rely on the knowledge-deficit model, which "presumes that one-way instruction of laypersons by experts will result in public support."[105] As the NAS report describes, the correct process must involve "'reflexivity' among participants, in the sense of creating opportunities for reflexive thinking to clarify one's beliefs and understandings, reflect upon and revise one's opinions, and gain insight into how different interests and values are situated in conversations about how to proceed."[106]

In the Mice Against Ticks project, Esvelt used the town hall-style decisionmaking process that the community was comfortable with in order to achieve consent by mutual learning.[107] In addition, engagement involved coverage by local media outlets, selection of a vocal skeptic to channel community concerns, and dispersal of an educational pamphlet designed by a local high school biology class.[108] Oxitec's proposed mosquito project in the Florida Keys provides another model, where referendums were held in both the county and on the specific island where the project would be deployed.[109] What it means to obtain consent is an issue that will vary from community to community, and every scientist engaging in wildlife gene drive research must develop a defendable strategy that brings procedural justice to the stakeholders involved.

CONCLUSION

The CRISPR gene drive technology has the potential to revolutionize how humans manage the natural environment. Given this profound

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103 *See* Buchthal et al., *supra* note 16, at 6.

104 *See, e.g.*, Grunewald, *supra* note 57, at 20 (noting that gene drive research could perpetuate the Global North/South divide).

105 NAS, GENE DRIVES, *supra* note 1, at 135.

106 *Id.*

107 Buchthal et al., *supra* note 16, at 6.

108 *Id.* at 7.

109 Braverman, *supra* note 3, at 66.

development, along with the fact that the technology's consequences are uncertain and its applications capture the public imagination, it is understandable for many to question it. In the past, conservation of nature was limited to the ecological level, but now gene drives make it possible for humans to tend to nature at the biological level. This power will prompt a fundamental shift in how humans value nature, though it is a necessary shift that humans must accept in the current Anthropocene. It is also important that scientists engaging in wildlife gene drive research learn how to effectively incorporate risk analyses and community engagement efforts, even though that is a daunting task for an area of scientific research where uncertainty reigns.