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RESEARCH ARTICLE

Genes drive organisms and slippery slopes

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ABSTRACT

The bioethical debate about using gene drives to alter or eradicate wild populations has focused mostly on issues concerning short-term risk assessment and management, governance and oversight, and public and community engagement, but has not examined big-picture — 'where is this going?'—questions in great depth. In other areas of bioethical controversy, big-picture questions often enter the public forum via slippery slope arguments. Given the incredible potential of gene drive organisms to alter the Earth's biota, it is somewhat surprising that slippery slope arguments have not played a more prominent role in ethical and policy debates about these emerging technologies. In this article, we examine a type of slippery slope argument against using gene drives to alter or suppress wild pest populations and consider whether it has a role to play in ethical and policy debates. Although we conclude that this argument does not provide compelling reasons for banning the use of gene drives in wild pest populations, we believe that it still has value as a morally instructive cautionary narrative that can motivate scientists, ethicists, and members of the public to think more clearly about appropriate vs. inappropriate uses of gene drive technologies, the long-term and cumulative and emergent risks of using gene drives in wild populations, and steps that can be taken to manage these risks, such as protecting wilderness areas where people can enjoy life forms that have not been genetically engineered.

KEYWORDS

Gene drive; CRISPR; slippery slope argument; ethics; regulation

1. Introduction

Selfish genetic elements are naturally occurring DNA sequences that bias inheritance in their favor so that they tend to increase in prevalence in a population, even if they negatively impact organismic fitness [1]. For more than sixty years, scientists have contemplated the possibility of using natural selfish genetic elements to control invasive or pest species and animal disease vectors, but technical challenges prevented these plans from coming to fruition [2–4]. The development of accurate and efficient gene editing tools, such as CRISPR (i.e. clustered regularly interspaced short palindromic repeats), has facilitated the construction of synthetic selfish genetic elements, commonly referred to as gene drives, and opened the door to engineering of wild populations [5–7]. [1]

The prospect of using gene drives to alter or suppress mosquito populations has generated considerable interest among scientists and public health officials as a strategy for controlling malaria and other mosquito-borne diseases [6–10]. Researchers have introduced a gene drive system that codes for an antibody against the malaria parasite into laboratory *Anopheles* mosquito populations [11]. In an experiment that served as a proof of principle, 99.5% of first-generation progeny from mating of genetically modified (GM) heterozygous mosquitoes with the wild type had the malaria antibody variant, although the gene drive broke down over a short time period [11]. Researchers have more recently shown that introduction of a gene drive system that biases chromosomal transmission in favor of the Y-chromosome in *Anopheles* mosquitoes led to nearly 100% males and population collapse in 10–14 generations [12]. Genetically modified organisms that incorporate gene drives (i.e., gene drive organisms or GDOs) have not yet been released into the wild, but that day could be approaching fast [7]. [2]

The potential public health, agricultural, and environmental benefits of using GDOs to alter or suppress wild populations are significant. GDOs could be used

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[1]Although CRISPR has received considerable attention in the scientific literature and the media, it is worth noting that other gene editing tools have been available since the 1970s and that more tools are likely to be developed in the future.[7].

[2]GMOs that do not incorporate gene drives have been released into the wild. Since 2009, Oxitec has conducted field trials of genetically modified (GM) *Aedes aegypti* mosquitoes in the Cayman Islands, Brazil, Malaysia, and the US. The current strains of Oxitec's GM mosquitoes, have a genetic mechanism that causes female offspring to die in the larval stage unless they are exposed to tetracycline, a commonly prescribed antibiotic that does not occur in the natural environment in high concentrations. When the males are continuously released and breed with female mosquitoes in the wild, the population declines, often dramatically. Because only males with the engineered trait survive, the trait is expected to eventually be lost from the population once releases are ended.[13,14].

Table 1. Potential beneficial uses of genes drive technologies in wild populations.

Use	Population Alteration Example	Population Suppression Example
Eradicate or control human or animal infectious diseases	Immunize animal vectors against various diseases, such as malaria, encephalitis, yellow fever, zika, rabies, and Lyme disease	Suppress animal disease vector species, such as mosquitoes, ticks, or white footed mice Suppress pathogenic or parasitic organisms, such as certain types of bacteria, fungi, or worms
Control invasive or pest species	Enhancing the fecundity or robustness of species that prey on invasive species.	Eradicate invasive rats, rabbits, squirrels, fire ants, social wasps, and other invasive species that disrupt ecosystems and threaten biodiversity
Protect endangered or threatened species	Immunize endangered or threatened species against diseases	Eradicate species that prey on or transmit diseases to endangered or threatened species
Promote agricultural productivity and sustainability	Decrease pesticide resistance in agricultural pests, including plants, insects, mites, and molds	Suppress agricultural pests, including plants, insects, mites, and molds
Control pollutants and toxins	Enhance the ability of plants, fungi, or bacteria to remove pollutants and toxins from the air, soil, or water	
Manage ecosystems	Enhance the ability of plants, fungi, and bacteria to enrich and retain soil or build sustainable ecosystems in inhospitable areas, such as deserts	
Mitigate climate change	Enhance the ability of trees, algae, plankton, and other plants to sequester carbon	

Table 2. Potential risks of using gene drive technologies in wild populations.

Type of Risk	Population Alteration Example	Population Suppression Example
Human health	Immunization of a human disease vector (such as a mosquito species) against a pathogen leads to evolution of a resistant pathogen	Eradication of a human disease vector (such as a mosquito species) allows another vector to take its place in the ecosystem
Ecological	Genetic enhancement of an organism destabilizes an ecosystem	Eradication or suppression of an invasive or pest species destabilizes an ecosystem
Ecological/ biosafety	Gene drive organisms with enhancement escape from the laboratory, become invasive species, and disrupt the ecosystem	Gene drive organisms developed to suppress populations escape from the laboratory and disrupt the ecosystem
Agricultural	Immunization of an agricultural disease vector against a pathogen leads to evolution of a resistant pathogen	Eradication of an agricultural pest species allows another pest species to take its place in the ecosystem
Biodiversity	Alteration of wild species leads to loss of biodiversity	Eradication or suppression of wild species leads to loss of biodiversity
Biosecurity	Alteration of wild species for biowarfare or bioterrorism; for example, modifying a species so it can transmit diseases to humans, animals, or plants	Eradication or suppression of wild species for biowarfare of bioterrorism; for example, eradicating a keystone species to trigger ecosystem collapse
Sociocultural	Alteration of a wild species without strong community, stakeholder, or public support leads to backlash, hostility, and resentment	Eradication of a wild species without strong community, stakeholder, or public support leads to backlash, hostility, and resentment
Political	Alteration of a wild species that cross national borders leads to political conflict	Suppression of a wild species that cross national borders leads to political conflict

to prevent human and animal diseases, enhance agricultural productivity and food security, protect endangered species, control invasive and pest species, decrease pollutants and toxins, manage ecosystems, and mitigate climate change [6,7,14–20]. (See Table 1.) However, GDOs also create significant risks for human health, agriculture, the environment, biosafety, biodiversity, and biosecurity [6,7,14,21–23]. (See Table 2.) Because GDOs have not been released into the environment, there are no empirical data pertaining to risks from field releases. Scientists have identified and assessed some of these risks by studying organisms in the laboratory and mathematically modeling ecological and public health effects [7,24,25].

The risks of using GDOs in wild populations are significantly different from those associated with agricultural or biopharmaceutical applications of genetic engineering because 1) the organisms will be deliberately released into the environment and may not be physically or biologically contained; and 2) in some cases the genetic changes to populations are likely to be pervasive and long-lasting or permanent [7]. Some GDOs that are accidentally or deliberately released could therefore become invasive species and disrupt or destabilize ecosystems [16,23,26]. Most GM crops which are accidentally released into the wild are likely to die out because the advantageous traits with which they have been equipped, such as herbicide resistance or insecticidal properties, often make them unfit outside of agricultural settings [27 28][3] Also, some early, experimental GM crops had incorporated gene use restriction technologies (a form of biological containment) that rendered their offspring infertile [27].

Researchers have proposed some strategies for minimizing the risks of using GDOs in wild populations, such as: deploying GDOs that are built to be geographically restricted and thereby prevent global spread; developing self-limiting gene drives that become inactive in a few years; incorporating susceptibility to chemical agents into GDOs so that they can be easily killed if necessary; and developing GDOs to counteract invasive or disruptive GDOs [5,7,14,16,23,27,29]. Since

[3]There are, however, some noteworthy cases in which GM plants have become invasive species. GM creeping bent grass, which is used as a turf for golf courses, is spreading uncontrollably across Oregon.[28].

these strategies have not been tested in the wild, their effectiveness is unknown [7,29].

While the ethical and policy debate about using gene drives in wild populations has been rich, imaginative, and varied, it has focused mostly on issues concerning assessment and management of short-term risks; public, stakeholder, and community engagement; and legal oversight [7,14,24,25,30–36]. However, there has been very little in-depth examination of big-picture or 'where is this going?' questions related to gene drives.[4]

In other areas of bioethical inquiry, big-picture questions often enter the public forum via slippery slope arguments [37–41]. For example, opponents of human germline editing have argued that we should not genetically modify the human germline, even to prevent serious diseases, because this will lead humanity down a slippery slope toward genetic enhancement, which could create numerous social and moral problems, such as eugenics, exacerbation of socioeconomic inequalities, increased discrimination against disabled people, and the devaluation of human life [38,39,41].

Two articles, one published in a science journal, and another in a bioethics journal, have raised slippery slope concerns about using GDOs in wild populations. In an interview published in *Pathogens and Global Health* in 2017, evolutionary ecology professor James Collins comments that using GDOs to eradicate mosquitoes that carry malaria 'puts us on a slippery slope in terms of what we might consider a pest. Not that we would say that malaria-bearing mosquitoes are just a pest, they are much more than that, but then you can pretty easily slide from there, it seems to me, to other kinds of species that you prefer not to have around.' [42] In a review article published in *Bioethics* in 2019, philosopher/ethicist Daniel Callies remarks that using GDOs on mosquito populations may one day 'lead to a completely designed world-one in which we use gene drives to construct all life, including the "perfect human".' [43]

Collins and Callies raise some provocative questions but do not pursue them in much depth. Given the incredible potential of GDOs to alter the Earth's biota, it is somewhat surprising that slippery slope arguments have not played a more prominent role in ethical and policy debates about these emerging technologies. Nevertheless, slippery slope concerns about GDOs may be lurking in the background even when they are not expressed explicitly.

For example, a survey of 1,018 US adults found that respondents were 22% less likely to support the use of unlimited GDOs in agriculture than self-limited GDOs, and they were 11% less likely to support using GDOs to target native species as opposed non-native species. Respondents indicated that public health and environmental impacts of GDOs were the most important uncertainties to resolve before deciding whether to use GDOs [44]. A survey of 1,600 US adults found that 70.8% of respondents were concerned that using GDOs in wildlife populations interferes with nature [45]. A survey of 8,199 New Zealanders found that attitudes toward GDOs are strongly influenced by worldviews and that information-driven public engagement is likely to be less effective at generating public support for GDOs than value-oriented engagement [46].

These surveys suggest that public attitudes toward GDOs may be shaped by moral qualms that extend beyond questions related to short-term risks and benefits and encompass big picture, value issues [47]. We believe, therefore, that it is important to examine slippery slope arguments in greater depth in order to think more clearly about these issues and promote effective public engagement. In this article, we will develop and critique a slippery slope argument against using GDOs to alter or suppress wild populations and consider whether slippery slope concerns have a role to play in ethical and policy debates concerning GDOs.

2. Slippery slope arguments

The phrase 'slippery slope' is a metaphor used to describe a progressive process in which short-term actions, which may not be harmful in themselves, produce long-term outcomes which are. Although slippery slope arguments deal with possible or probable outcomes of decisions or policies, they are different from traditional risk/benefit analyses because 1) they do not involve any explicit weighing of risks and benefits; and 2) they generally focus on future harms that may occur cumulatively and emergently, and perhaps even unnoticeably, over a long period of time.

Philosophers have distinguished between several forms of the slippery slope argument [37]. A common version of the argument is as follows:

(1) Engaging in practice X will initiate a psychological, social, or economic process that is likely to lead to outcome Y.
(2) Y is morally objectionable.
(3) Therefore, to avoid this morally objectionable outcome, we should not engage in X or permit X to be done.

The process that creates the slippery slope may involve changes in attitudes, beliefs, behaviors, or policies that occur over time. For example, some have argued that we should not legalize physician-assisted suicide because doing so will cause laypeople and

[4]A notable exception here are Kuzma and Rawls, who consider the development of gene drive technologies and our obligations to future generations.[36].

physicians to start de-valuing human life, which will lead to practices we regard as morally abhorrent, such as involuntary euthanasia [48]. The type of slippery slope argument schematized above is an empirical argument, because support for its conclusion depends on empirical claims about causal or statistical connections between human behaviors and adverse outcomes. Therefore, facts and theories from the social and behavioral sciences and other disciplines often have a bearing on the strength of this type of argument [49,50]. For example, evidence concerning steadily increasing rates of physician-assisted suicide in countries that have legalized this practice is regarded by many as supporting the slippery slope argument against legalization of physician-assisted suicide [51].

Even when slippery slope arguments lack empirical support they can be rhetorically and politically effective because they appeal to our fears and aversions to risks and uncertainties [52]. Consequently, slippery slope arguments can frame public discourse and influence legislation and regulation [41]. For these reasons, slippery slope arguments that seem implausible to some should still be taken seriously.

3. A slippery slope argument against using gdos in wild populations

Now that we have discussed the nature of slippery slope arguments, we can construct a slippery slope argument against using GDOs in wild populations. The first step is to conceive of an outcome that many people would find to be morally objectionable. While there are an indefinite number of possible outcomes that could fill this role, below are three different scenarios worth considering:

3.1. Bioengineered world

Using GDOs to alter or suppress wild pest populations is likely to lead to human genetic modification of a substantial proportion of the Earth's biosphere.

3.2. Bio-armageddon

Using GDOs to alter or suppress wild pest populations is likely to lead to widespread use of GDOs for terrorism, crime, and warfare.

3.3. Ecological catastrophe

Using GDOs to alter or suppress wild pest populations is likely to result in GDOs that eradicate keystone species, resulting in ecological disasters, such as mass extinctions or collapsing ecosystems.

While we refer to these as 'different' scenarios, they are not mutually exclusive. For example, biowarfare, bioterrorism, or bio-crime could lead to ecological catastrophes; or ecological catastrophes could exacerbate competition for natural resources and increase the risk of biowarfare, bioterrorism, or bio-crime. Even so, we think it is useful to distinguish between these types of scenarios because they raise different ethical and policy issues.

Although we think that these scenarios are all worth reflecting upon in debates about GDOs, we will focus on the bioengineered world scenario in this paper because it raises more unresolved ethical and policy issues than the other two scenarios.[5] There is very little disagreement about the importance of preventing GDOs from causing ecological disasters or being used for terrorism, crime, or warfare. Scientists and policymakers are already concerned about these problems associated with GDOs (and other applications of biotechnology) and are deliberating about steps that can be taken to prevent them [7,22,23,53–56]. However, it is not obvious that a bioengineered world would be morally objectionable to people who are not opposed to genetic engineering for religious or philosophical reasons. Moreover, determining what would or could be morally objectionable about such a world requires careful ethical analysis and reflection that may lead to some insights that are not currently being considered in policy debates about GDOs.

With the foregoing in mind, let's suppose that someday biological science and technology advance to the point where we have the ability to modify or eliminate almost any wild or domestic species on Earth and we choose to exercise that power to reshape the biosphere according to our plans, needs, and desires. In short, imagine a world in which a significant proportion of life on Earth has been bioengineered to serve public health, agricultural, environmental, economic, aesthetic, or other purposes.

We can now formulate a slippery slope argument against using GDOs in wild populations:

Premise 1: Using GDOs to alter or suppress wild pest populations is likely to lead to human genetic modification of a substantial proportion of the Earth's biosphere.

Premise 2: A world in which a substantial proportion of the Earth's biosphere has been genetically modified by human beings would be morally objectionable.

Conclusion: Therefore, to avoid this morally objectionable outcome, we should prohibit GDOs from being used to alter or suppress wild pest populations.

Is this a good argument? Should it play a role in public policy and discourse about GDOs? We will now address these questions.

[5]The other two scenarios could be topics for other papers.

4. Is using GDOs to alter or suppress wild pest populations likely to lead to human genetic modification of a substantial proportion of the Earth's biosphere?

The first step in evaluating this slippery slope argument is to consider evidence that the slide down the slope is likely to occur, since there is little point in worrying about an outcome that has only a slim chance of happening. A key word that needs to be clarified is 'substantial.' We will not attempt to quantify this word in terms of the total percentage of the biosphere that is genetically engineered or some other measure. Rather, we will interpret 'substantial' as a proportion that is large enough to raise moral concerns for many people who are not opposed to GMOs in principle.

With this clarification in mind, we can consider the evidence for a slippery slope. A moment's reflection on the history of technology suggests that using GDOs in wild pest populations will likely lead to increased and expanded use. Printing presses, guns, steam engines, chemical explosives, radios, automobiles, airplanes, radar, televisions, antibiotics, computers, and many other technologies spread from their original applications to numerous others, despite any moral misgivings people may have had about using them [57]. Economic, social, and political forces often play a key role in accelerating the development and spread of new technologies. Gene drives, and biotechnologies more generally, are no different from other technologies in this respect. Furthermore, we have evidence that genetically modified organisms (GMOs) have already transformed agriculture so that 90% of corn, cotton, and soybeans grown in the US are genetically modified, which shows that GMOs can quickly dominate agricultural landscapes [58].

The slide down the slippery slope toward widespread use of GDOs in wild pest populations might start via expansion of the classification of a 'pest' species [42]. 'Pests' could be labeled as such because they pose a threat to agriculture, public health, or ecosystems. Genetic engineering of wild pest populations could begin with species that pose a significant threat to public health, such as mosquitoes that carry malaria or ticks that carry Lyme disease [20]. Once this door is open, there would be a strong rationale for genetic engineering of species that threaten agriculture, such as Japanese beetles and locusts, and then invasive species that threaten ecosystems, such as various rodents in New Zealand [6,59,60]. The next key step down the slope would be to start using GDOs for other public health, agricultural, or environmental purposes, such as improving soils, stabilizing ecosystems, mitigating climate change, or filtering air and water pollutants. (See Table 1.) At the end of the slope would be using GDOs for economic, recreational, aesthetic, national security, or other purposes [6]. (See Table 3.).

Some of the steps described above have already been taken place and others are underway [6,7]. Once humanity starts using GDOs to alter or suppress wild pest populations, there will be a strong impetus to exploit this technology and expand the scope of its application. What could stop this slide?

Government regulation and control would seem to be the most likely way of curtailing the slide toward widespread use of GDOs in wild populations. Most industrialized nations have governance systems in place for regulating GMOs that could be applied to GDOs [61,62]. For example, Oxitec's GM mosquitoes were reviewed and approved by regulatory agencies in the US, Brazil, the Cayman Islands and Malaysia [13,63]. [6] At the global level, there are international legal frameworks, most notably the Cartagena Protocol on Biosafety to the Convention on Biodiversity, which can be applied to GDOs. The Cartagena Protocol, which has been adopted by 173 nations, establishes international standards for handling, transporting, and using GMOs that can impact biodiversity and public health [64]. The Protocol has played an important role in promoting biosafety worldwide and responsible development and use of GMOs [62]. In 2018, parties to the Protocol considered but did not approve a moratorium on the use of GDOs in wild populations [65]. Additionally, the World Health Organization (WHO) regularly convenes scientific groups to provide guidance on responsible development and use of biomedical technologies. For example, in 2014 the WHO issued an influential report on using genetically modified mosquitoes to combat malaria, including mosquitoes that incorporate a gene drive [66]. Although the WHO is not a regulatory body, its recommendations can influence international cooperation on biomedical issues.

While the potential exists for nations, individually and collectively, to regulate and control the use of GDOs in wild populations, there are some reasons to doubt the effectiveness of these efforts. First, there are significant gaps in biotechnology regulations adopted by many countries [67,68]. For example, in the US and other industrialized nations biotechnology products that are not intended to be commercialized may go unregulated. Amateur, do-it-yourself genetic engineers (or 'biohackers') present an especially difficult regulatory challenge because they tend to be fiercely independent and opposed to regulatory oversight [69,70].

Second, most government regulations of GMOs focus on assessment and management of short-term

[6]Oxitec's mosquitoes do not incorporate a gene drive system. See note 7.

Table 3. Ethically questionable or malicious uses of genes drive technologies in wild populations.

Use	Population Alteration Example	Population Suppression Example
Commerce/ industry	Alter wild populations to increase their marketability or to streamline industrial processes to reduce production costs	Suppress wild populations to facilitate commercial activity or industry; e.g. suppressing bird populations to facilitate wind power or air travel
Aesthetics	Alter wild populations to make them more aesthetically appealing; e.g. changing the coloring of birds, mushrooms, or trees	Suppress populations that one regards as distasteful or unappealing; for example, suppressing rat and opossum populations
Recreation	Alter wild populations for recreation; e.g. changing the behavior of some animal species to enhance the hunting experience	Suppress wild populations for recreation; e.g. suppressing sharks to make it safer to swim in the ocean
Biowarfare or bioterrorism	Enhance the ability of vector species to carry deadly human or animal diseases	Suppress agriculturally or ecologically important plant or animal species

environmental or public health risks, rather than on issues related to long-term risks, social impact of GMOs, or control of uses [34,35]. For example, the EPA's approval process for Oxitec's GM mosquitoes focused on short-term environmental and public health risks and did not address ethical questions about whether this was a socially acceptable use of genetic engineering [71].

Third, the Cartagena Protocol has some significant deficiencies. The Protocol lacks strong enforcement mechanisms and does not address questions concerning socially acceptable uses of GMOs and self-initiated movement of GMOs across borders and lacks strong enforcement mechanisms. Also, the leading country in biotechnology innovation, the US, has not signed to Protocol [70,71].

Fourth, international cooperation on GDOs may be difficult to achieve or sustain, given the economic and social incentives to abjure from or violate treaties that restrict gene drive technologies [64]. Even if many countries significantly restrict GDOs, scientists, bioengineers, and companies may decide to move to countries with friendly and supportive regulatory, economic, and social environments, as has occurred with other biomedical technologies [72].

While it is likely that governments will work together to control the use of GDOs in wild populations, the effectiveness of these efforts in preventing the bioengineered world scenario is difficult to predict. A great deal depends on whether the public exerts pressure on governments to regulate GDOs and whether there are strong economic, social, or political forces that work against concerted action on GDOs. The history of international cooperation on public health and environmental issues does not give a clear indication of whether countries will be able to control the use of GDOs, because the international community has had a mixture of successes (such as control of stratospheric ozone depletion and persistent organic pollutants) and failures (such as climate change and nuclear proliferation) regarding such matters [73–76]. Given these uncertainties, the idea that using GDOs in wild pest populations will someday lead to genetic modification of a substantial proportion of the Earth's biosphere is a real possibility that should be considered in public policy concerning GDOs.

5. Would a world in which a substantial proportion of the Earth's biosphere has been genetically modified by human beings be morally objectionable?

If a slide down the slope toward a bioengineered world is likely to occur, the next question to ask is whether this situation would be morally objectionable. In approaching this question, we will not focus on objections from those who are opposed to all forms of genetic engineering, or at least to genetic engineering of plants and animals.[7] People who take this position, often for religious or philosophical reasons, would morally object to a world in which human beings have genetically modified even a negligible proportion of the biosphere [27,78–82]. People who hold this view would presumably regard a world that has been extensively genetically engineered to be far more objectionable than one that has only been marginally genetically engineered. However, slippery slope concerns do not change the basic moral outlook of those who have zero tolerance for GMOs because they would regard any use of gene drive organisms in wild populations as immoral. We are more interested in whether those who accept some genetic engineering of wild populations would have moral qualms about genetically engineering a substantial proportion of the biosphere.

If we assume that genetically engineering a substantial proportion of the biosphere does not lead to ecological catastrophes or other environmental or public health problems, it seems to us that the main moral concern with the bioengineered scenario would be that people would have limited or perhaps no access to non-genetically engineered ('natural'), wild populations.[8] Many people would regard loss of access to non-genetically engineered wild populations as a

[7]This type of opposition is sometimes expressed as the view that genetic engineering is 'playing God.'[27],[46] We will not examine that position in-depth here. It is likely that people have fundamental disagreements about the morality of GMOs than cannot be easily resolved by rational arguments or empirical evidence and that the best way forward may be to try to reach procedurally fair, political solutions that recognize the interests of different parties and allow for meaningful engagement in public decision-making.[88].

[8]We use 'natural' in scare quotes here because there are significant scientific and philosophical questions about what makes something natural or unnatural [81,83,88]. Some people refer to non-GMO corn as natural, but non-GMO corn is the product of hundreds of years of

moral tragedy because they would like to experience and appreciate the beauty of unspoiled nature [81]. Allowing a substantial proportion of the biosphere to be genetically engineered would therefore cause significant harm to present and future generations who would like to have access to these resources.[9] [34,36]

A key moral question here is whether – or to what extent-one should regard unspoiled nature as a valuable resource that should be preserved. This is not a new question in environmental ethics and policy. An assortment of environmental issues, including, land use, energy extraction, and agricultural and urban development, reflect a tension between preserving and exploiting nature.[87] [83–85], While the issues raised by the bioengineered world scenario are not entirely new, they do raise some novel questions about what constitutes 'unspoiled nature' or why we should care about it [81]. Most people regard the environment as a valuable resource because it can provide humanity with material things needed to sustain life, health, and economic prosperity, such as clean air and water, food, fuel, and so on [77]. Some also view the environment as important for non-materialistic purposes; for example, as a source of moral, aesthetic, or spiritual inspiration; as a place to meditate or relax; to commune with nature; and so on [81,86,87]. Even if genetically engineering a substantial proportion of the biosphere does not interfere with the capacity of the environment to serve as a material resource, it might interfere with the interests of those who regard it as important for non-material purposes. Respecting this viewpoint implies that there is an obligation to take appropriate steps to protect these interests.

If there is an obligation to protect the interests of those who would like to have access to non-genetically engineered, wild populations, species, and ecosystems, does it imply that we should never introduce GDOs into wild pest populations? This is a difficult question to answer because it involves balancing the interests of those who want access to GMO-free wild populations against the interests of those who may benefit from using GDOs on wild pest populations. Since we live in a society in which people hold diverse moral, philosophical, and religious values, the most reasonable way forward may be to pursue compromise solutions that acknowledge the interests of those who want access to GMO-free nature and the interests of those who want to use GDOs to promote public health or other worthy goals [77,88]. For example, a nation or state could balance these competing interests by setting aside 'GMO-free' tracts of land for posterity, much in the way that nations establish national parks and wilderness areas. We do recognize, however, that it may be difficult to maintain these 'GMO-free' zones because GDOs may contaminate these areas. Accordingly, careful thought and planning will be needed to establish and maintain these zones. We also recognize that 'GMO-free' zones are not likely to satisfy people who hold a zero-tolerance view concerning GMOs.[10] Despite these concerns, it seems like it would be reasonable and fair to try to set aside and protect GMO-free wilderness areas if there is sufficient demand for them.

6. Discussion and conclusion

In this article, we have examined a type of slippery slope argument against using GDOs in wild pest populations that contemplates the prospect of a bioengineered world as the endpoint of the slope. In our critique of this argument, we argued that while using GDOs in wild pest populations could lead to genetic modification of a substantial proportion of the Earth's biosphere, the extent of this modification depends on political, economic, and social factors that are difficult to predict. We also argued that the chief moral objections to the bioengineered world scenario can be met by taking actions to preserve and protect 'GMO-free,' unspoiled wilderness areas.

Although the type of slippery slope argument we have examined in this paper (i.e. the bioengineered world at the downside of slope) does not provide compelling reasons for prohibiting the use of GDOs in wild pest populations, other versions of the slippery slope argument (e.g. ecological catastrophes at the downside of the slope) might. Additionally, our analysis raises some important ethical and policy issues and has value as an instructive cautionary narrative that can motivate scientists, ethicists, and members of the public to think more clearly about big-picture questions, such as appropriate vs. inappropriate uses of gene drive technologies and managing the long-term, cumulative, and emergent risks of using gene drives in wild populations. Our reflections on slippery slope concerns related to GDOs support the following policy recommendations:

- Reform biotechnology laws and regulations to close loopholes and address issues not currently covered, such as appropriate vs. inappropriate uses of GDOs and long-term risks.
- Reform biotechnology treaties and improve international cooperation on GDOs.
- Ensure that local communities and other affected stakeholders have meaningful involvement in GD-GMO decisions that affect them.

selective breeding. In a sense, everything made by human beings is natural because human beings are part of nature.

[9] We also note that non-engineered species and ecosystems could serve as a repository of valuable genes for breeding programs.

[10] See note 7.

- Engage the public about appropriate vs. inappropriate uses of GDOs in wild populations (see Tables 1 and 3).
- Take appropriate measures to prevent the use of GDOs for terrorism or warfare, such as developing professional guidelines or statements and enhancing biosecurity surveillance.
- Improve biosafety to avoid accidental release of GDOs.
- Use GDOs to enhance biodiversity in wild populations.
- Create and maintain repositories for biodiversity, such as seed and gene banks.
- Take steps to avoid destabilizing ecosystems when using GDOs in wild populations, such as introducing them gradually and studying ecological impacts.
- Establish 'GMO-free' wilderness areas where people can enjoy life forms that have not been genetically engineered.

Before concluding, we need to mention some important limitations of our analysis. First, we only addressed the bioengineered world outcome as a possible endpoint of the slippery slope and did not examine other possible outcomes that would be morally objectionable, such as ecological disasters or using GDOs for terrorism, crime, or warfare. Since we believe that these other scenarios are worth considering, we encourage other scientists and scholars to investigate them and explore their ethical and policy implications. Second, we have focused, for the most part, on ethical and policy issues and have not addressed political ones, such the role of expert opinion and public deliberation in policy formation and governance of GDOs. Clearly, these are important issues that must be dealt with no matter what stance one takes on slippery slope on other ethical concerns with GDOs.

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DBR, FG, JK, and RFM have no competing interests to disclose. GC does not have any financial interests directly related to this work but has filed patents on CRISPR and on RNA guided Gene Drives.

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Author contributions

DBR and JK conceived of the research project. DBR, FG, JK, RFM, and GC drafted and critically revised the manuscript.

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