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# A Code of Ethics for Gene Drive Research

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## Abstract

Gene drives hold promise for use in controlling insect vectors of diseases, agricultural pests, and for conservation of ecosystems against invasive species. At the same time, this technology comes with potential risks that include unknown downstream effects on entire ecosystems as well as the accidental or nefarious spread of organisms that carry the gene drive machinery. A code of ethics can be a useful tool for all parties involved in the development and regulation of gene drives and can be used to help ensure that a balanced analysis of risks, benefits, and values is taken into consideration in the interest of society and humanity. We have developed a code of ethics for gene drive research with the hope that this code will encourage the development of an international framework that includes ethical guidance of gene drive research and is incorporated into scientific practice by gaining broad agreement and adherence.

## Introduction

Modern societies that foster new technologies must also ensure that their agendas are openly communicated, discussed, and negotiated among scientists and the public.[1] One approach to help ensure that dialogue happens is for scientists to proactively develop a code of ethical conduct with special emphasis on one or more scientific agendas. Ethical codes are a way professionals assure the public that they will act in the best interests of society rather than in their own or that of their employer. Codes are, at least in aspiration, a tool to help scientists ''do the right thing'' by raising awareness of ethical challenges and providing at least some guidance for dealing with them.

At the dawn of an era in which gene drives are advancing toward applications in the field, it is increasingly important that scientists developing these technologies adopt and agree to follow a code of conduct to reassure the public (and themselves) that ethical values will be at the core of their actions. The SARS-CoV-2 pandemic has illustrated the fragility of the relationship between science and the public. Scientists have a responsibility to inform and counter public mistrust, unfounded rumors, and conspiracy theories, and a public pledge can be one tool to encourage science's constructive engagement with the public.

Gene drive technology enables certain genetic elements or the chromosomes that carry them to bias

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their own inheritance, thereby spreading a genetic trait through a whole population or an entire species in a relatively short time frame. Depending on the nature of this trait, the affected population can either be transformed or brought to suppression. Gene drives hold promise for use in controlling insect vectors of diseases or agricultural pests or for conservation of ecosystems against invasive species. At the same time, this technology inherently comes with potential risks that include unknown downstream effects on entire ecosystems as well as the accidental spread of organisms that carry the gene drive machinery.[2] Given the potential large-scale impacts of gene drives, there is an active discussion on the use and regulation of gene drive-modified organisms within the scientific community.[3] Particular emphasis has been placed on the distribution and dissemination of recommendations and guidelines on the research and development of gene drives. In this context, a code of ethics can be a useful tool to follow for all parties involved in gene drive research and can be used to help ensure that a balanced analysis of risks and benefits is taken into consideration for the interest of society and humanity. This approach will help ensure that the good uses of the technology are maximized and that less desirable or dangerous uses are minimized. A code also has advantages over a legal framework in that it can be developed and adopted faster and over multiple jurisdictions, and can be implemented by self-regulation and disciplinary action against individual violators of the code. To be meaningful, the terms used in a code must be general enough to have wide applicability, yet specific enough to guide conduct, and hold scientists accountable.

As members of the Controlling and Countering Gene Editing in Mosquitoes (C2-GEM) research project funded by the Defense Advanced Research Projects Agency (DARPA) Safe Genes program, we undertook to develop a code for gene drive research as part of this funded effort. Much of our work to develop a code was built on the guidelines for research oversight that have been suggested by various national panels, and we have found it useful to review their conclusions as a first approximation of the primary values at stake in gene drive research.[1] From these reports, we identified three recurring values that we believe are most relevant to research on gene drives: responsible science, ecological stewardship, and public engagement (including fair distribution of risks and benefits).[2,4–6]

Most of the work on the ethics of research has revolved around obtaining the informed consent of the individual subject. In contrast, current gene drive research has

been designed to modify the environment in which humans live, and individuals cannot provide consent for this research. For gene drive research involving the planned release of gene drive-modified organisms into the environment, it is more accurate to conclude that values most at stake in human research, including respect for persons, including human dignity and equity, are not central. The release of gene drive-modified organisms requires community consultation or agreement, rather than individual consent, one-by-one.[7]

There are, nonetheless, some basic values that apply to both broad categories of research. The language of human rights, for example, encompasses both the state's obligation to respect the bodily rights of physical integrity and autonomy, and the state's obligation to provide its citizens with clean air, clean water, and a healthy living environment. Human rights are birth rights[8] (i.e., all humans are born with them), which is one reason why the United Nations founded its Universal Declaration of Human Rights on the concept of "human dignity." Human rights doctrine holds that that humans inherently have dignity, which prevents them from being used as a means (rather than an end in themselves), and includes the obligation of states to respect, protect, and fulfill these human rights.[9]

## Values at Stake

*Responsible science* can be contrasted to irresponsible science, including science that is not peer reviewed or done in isolation and science that is predictably dangerous. In the medical profession, for example, the short hand statement, "first do no harm" is a direct way for a physician to pledge to always act in the best interest of their patient (although, of course, it really means do not intentionally harm. It permits taking chances, with the patient's consent, where the predicted benefits of an action outweigh its risks). The related "precautionary principle" in science can be seen as requiring a reasonable environmental risk/benefit analysis before a research project is launched that shows that the potential risks of a project are outweighed by its likely benefits—especially one that has the potential for modification of ecosystems, such as the intentional or unintentional release of gene drive-modified organisms such as mosquitoes, or even a novel virus.[10] One challenge, of course, is identifying and quantifying comparable risks and benefits. Potential risks include intentional modification to create harm, and failures of biosafety and biosecurity measures to prevent harm. Of course, international treaty law, including the Biological Weapons Convention, must be respected not only by states, but by

individual scientists as well. Responsible science also includes holding the actions of fellow scientists to the same high standards as one's own work. The scientific community should strive to create an environment in which irresponsible science is disincentivized on multiple levels, including sanctions by scientific journals, science funders, and fellow scientists. George Church, for example, has suggested that post-9/11, a responsible ethic for scientists to follow to decrease the likelihood of nefarious research is to call out dangerous experiments in a ''see something, say something'' check on their fellow scientists.

*Ecological stewardship* is a recognition that we are all responsible for the long-term health of the planet, and that our actions should not damage Earth's ecology in a way that cannot be remediated. Protection of ''endangered species'' and the maintenance of ecological balance also fit under this principle, as do proposals to require environmental impact statements on proposed organism release experiments.

*Public engagement* is widely accepted in principle, but there is no bright line test to determine exactly when engagement with the public should occur—except to observe that it should be as close to the initiation of a project as is practical and reasonable. This issue has been discussed in the literature.[11,12] Among the questions still to be determined in the context of gene drive-modified organism release studies are: what is the relevant ''public'' or community; who speaks for the public; what, if any, educational programs should be implemented as part of public engagement; which entities will be responsible for engaging with the relevant communities; and what is the proper forum for such engagement? It is also worth considering whether ''transparency'' is inherently a part of public engagement (we think it is). Moreover, if genetic modification of insects is inherently an international concern (since containment of modified insects to any one country may not be possible), then international institutions such as the World Health Organization (WHO) should take a leading role in governing gene-drive releases.

Public engagement also assumes another value that is often listed separately: *fair distribution of the burdens and benefits* of the research. This issue seems somewhat abstract in the gene drive research realm. It is, however, an issue that took center stage worldwide in the global discussion of determining which populations should have initial access to a safe and effective SARS-CoV-2 vaccine, and in what priority ranking.[13] This example may be used to spark discussions in other fields, including research related to gene drives.

The National Academies' *Gene Drives on the Horizon* report concludes that:

Research institutions, regulators, and funders should revisit international regulatory frameworks, national laws, non-governmental policy, and *professional codes of conduct on research* and the release of genetically modified organisms to determine whether and how they may be applied to the specific context of gene drive research, particularly with regard to the site selection issues, capacity building for responsible and inclusive governance systems, scientific and post release surveillance, and stakeholder engagement. (Emphasis added)[5]

## Other Relevant Codes

We reviewed all the major relevant codes of professional conduct that currently exist. Our goal was to determine if any existing professional codes cover these values, and if not, if one could be modified to apply to gene drive researchers. It was also important to us to identify and acknowledge the limitations of existing codes. As the *Gene Drives on the Horizon* committee put it: ''Professional codes of conduct that address technical and ethical considerations in research are an important source of governance that helps both to promote awareness among researchers and encourages them to take responsibility for their science.''[5] On the other hand, a WHO report on dual-use research has cautioned that codes will not deter bad actors determined to act outside the system and cause harm.[14]

Scientific codes of conduct have historically been adopted by professional groups to (1) respond to scandals by promising to try to do better; (2) to establish the ''moral credibility'' of a field; and (3) to provide a profession with a ''moral compass'' by setting forth its ideals.[7,15] As there is no gene drive research scandal we are responding to, it seems reasonable to categorize our quest for a code as providing a ''moral compass'' for gene drive researchers.

Scientists can, we think, constructively profess their beliefs in relevant standards of research ethics by affirming their acceptance of a *code of conduct* (sometimes referred to as an ethical code) that summarizes them. A code of conduct can also set ethical standards for scientific communities facilitating the recognition of research that does not meet these standards and thereby enabling concerted action against unethical science by, for example, denying publication and funding. Other commentators have persuasively suggested the Hippocratic ''do no harm'' principle can usefully be adopted by scientists. For example, in the aftermath of 9/11, a new ''Code of Ethics for the Life Sciences'' was suggested by Somerville and Atlas, the first principle of which is ''to work to ensure that their discoveries and knowledge do no harm…''[8,16]

> ### Box 1: Code of Ethics for Gene Drive Research
> I will conduct and apply my work on characterizing, optimizing, manipulating, or counteracting gene drives consistent with the needs and interests of humanity, with respect for human dignity and human rights, and holding paramount public health, public safety, and ecological stewardship. I am committed to the fair distribution of risks and benefits of gene-drive research, and to practicing science that is transparent and reproducible.
>
> #### Scientific responsibility
> I will work to ensure that my research, discoveries, and knowledge do no harm by (1) taking steps to minimize the risk of my research being misappropriated by others who might use it to cause harm, including refusing to engage in research that is intended to facilitate or that has a high probability of being used to facilitate bioterrorism or biowarfare or to violate the Biological Weapons Convention; (2) never knowingly or recklessly contributing to the development, production, or acquisition of biological agents or toxins; and (3) continuously assessing risks throughout the research process, from gauging risks before release to monitoring effects after release, and disclosing promptly factors that might endanger individuals, society, or the environment.
>
> #### Ecological stewardship
> I will work to identify, minimize, and justify any adverse effect my work may have on the public's health, animal and plant life, and the natural environment. This may include partnering with experts necessary to carry out this duty.
>
> #### Public engagement and benefit sharing
> I will ensure that my work proactively incorporates ecological risk assessment and informs a structured decision-making process to consider gene drive-modified organisms and any proposed field test or environmental releases. This process will include wide-ranging public discussions, begun as early as reasonably practical in the planning process, especially with the populations most likely to be directly affected. The discussions should incorporate likely scenarios, the potential for unforeseeable risks, and methods to contain or reverse genetic modifications and the likelihood of their effectiveness. Public engagement will include a consultation process that honestly and transparently identifies the burdens and benefits to the community.

The World Medical Association updated its 1948 Declaration of Geneva to read in part: ''I will respect the autonomy and dignity of my patient…I will not use my medical knowledge to violate human rights and civil liberties, even under threat.''[17] Similarly, the Institute of Electrical and Electronics Engineers (IEEE) Code of Ethics includes a pledge: ''To hold paramount the safety, health, and welfare of the public, to strive to comply with ethical design and sustainable development practices, and to disclose promptly factors that might endanger the public or the environment…''[18] AAAS recently published a one-paragraph code of ethics for scientists that reads in part: ''Scientific responsibility is the duty to conduct and apply science with integrity, in the interest of humanity, in a spirit of stewardship for the environment, and with respect for human rights.''[19]

Our proposed code is published here for adoption by those who find it useful as setting an ethical guide for gene drive research. Of course, as with all ethical guidance, it is a work in progress. The Code has to be strong enough to provide useful ethical guidance while remaining flexible enough to adapt to changing facts and data. In this regard, its inherent vagueness (which we concede is a limitation) will move toward specificity as the code itself is applied to real-world research and a sort of ''common law ethics'' is developed on a case-by-case basis. Our hope is that this code is a first step toward implementing an international framework that allows for ethical guidance of gene drive research and that is incorporated into scientific practice by gaining broad acceptance and adherence.

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**Box 2: Methods—Developing the Code of Ethics for Gene Drive Research**

The approach we used was a normative analysis supplemented with a modified Delphi set of regular monthly discussions with the C2-GEM scientific team, each revisiting past conclusions and modifying or adding to them. We began with an examination of values that leading national commissions and committees have identified, determined where they agree with each other, and used these overlapping lists as a first approximation of critical values that may be relevant to gene drive research.

In research that does not directly make use of human subjects, such as research on animals and insects, different values and considerations may be at stake, although some, such as basic human rights, overlap. We concluded that on the surface at least, the values having the most relevance to gene-drive mosquito research are as follows: Responsible science, ecological stewardship, and public engagement. While this exercise was ongoing, a preliminary list of values was supplied to team members in June 2017. Asked which they believed are most relevant for their projects, the members of the C2-GEM team put responsible science first, environmental impact and community engagement second, and transparency third (we later incorporated this value into community engagement). Some also added concern over dual use/bioterrorism as a critical consideration. Biosecurity/biosafety concerns include (1) unintended and unforeseen consequences of release, (2) release due to negligence or natural disasters, and (3) intentional release or misuse. In response to this survey, team members also agreed (9:1) that ''developing an ethical code should be a priority'' and that using scenarios in planning future research could be useful.

Thoughts on specific values were also solicited in June 2017, and again in May and June 2018, to determine if there have been any shifts in emphasis. The reconsideration was done by group discussion, following what can be described as a modified Delphi discussion, rather than a resurvey of the team members. We reviewed the draft document again in 2019 and 2020. A draft of this code was distributed among selected members of the gene drive scientific community for comment, and we then reviewed it again, giving it a final review on the basis of reviewer comments. We also published an earlier version in the legal literature (in the context of the human genome editing scandal in China) for comments.[9]

We discussed each of our three central values, responsible science, ecological stewardship, and public engagement, in some detail. We reached a consensus that responsible science included safety, security, peer review, and data sharing. Ecological stewardship included a risk assessment, as well as attention to sustainability, stewardship, and conservation of biodiversity. Public engagement remains perhaps the most difficult to define, but is related to transparency and the informed agreement of an identified population. ''Education'' does not mean simply explaining the project, but engaging the relevant population in a discussion of its risks and benefits to them as well as a meaningful opportunity to accept or reject the project for their community. In reviewing the overall listings again, there was also consensus that ''fair and equitable sharing of benefits'' should be added to our final list of values, and that this value would naturally pair with public engagement.

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## Authors' Contribution

All authors contributed to the article.

## Author Disclosure Statement

## Disclaimer

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