Gene Drive Research Forum
Unsettled Ethical Issues in Gene Drive Research

Organizers: GeneConvene Global Collaborative
            McMaster University Institute on Ethics and Policy for Innovation (IEPI)

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Overview

The Gene Drive Research Forum hosted a series of virtual panel discussions focused on unsettled ethical issues important to gene drive research. The series brought together stakeholders from research, government, private sector, and not-for-profit organizations, as well as other parties with an interest in safe and ethical conduct of gene drive research for applications in public health, conservation, and agriculture. Over the course of four sessions, the panelists considered a variety of topics related to ethical issues and emerging technologies, including the moral differences of the natural and synthetic; considerations of justice and equity; the nature and scope of obligations of various actors in the gene drive space; and the role of principles in the ethical governance of emerging technologies such as gene drive.

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Panel 1: Natural and synthetic

The moral and ethical considerations of the natural vs. synthetic debate have implications for the development, application, and governance of gene drive technologies. Throughout the discussion, the panelists examined the ethical implications of the duality of the natural and synthetic in relation to emerging technologies, while also suggesting that this distinction alone is insufficient for determining the ethical status of gene drive technologies. While one panelist questioned the power dynamics surrounding a preoccupation with the natural/synthetic divide, another affirmed the importance of considering the moral difference between the natural and the synthetic when it comes to interventions in shared environments.

Key themes from this discussion:

- The boundaries between the terms "natural" and "synthetic" are ill defined, but the reasoning behind this attempt at categorization highlights important moral considerations.
- Human-designed technologies that rely on biology blur the line between natural and synthetic interventions.
- Focusing on justice, human rights, and humans' responsibility to protect nature helps to reframe questions that too easily trigger debates about the natural vs. the synthetic.

Panel 2: Justice and equity

The panelists addressed issues of justice and equity in relation to the development and potential deployment of gene drive, primarily in the context of global health applications. While emphasizing the importance of exploring gene drive as a means of tackling global health disparities (e.g., malaria burdens), the panelists acknowledged the challenges in designing and implementing practical approaches to achieve equity in outcomes. The panelists agreed that focusing on ethical research governance and reducing disparities in research capacity between the Global North and other countries is essential for expanding justice and equity in gene drive research.

Key themes from this discussion:

- To the extent that gene drive is an intervention that may reduce existing health inequities, researchers have a moral obligation to fully explore potential applications.
- Geographic disparities in research capacity and governance underlie concerns of justice and equity in gene drive research and development.
- Alternative approaches and forums for practically engaging with questions of justice and equity in gene drive are needed.

Panel 3: Who owes what to whom?

The panelists confronted the varied nature and vast breadth of obligations bound to the development of gene drive technologies, with an emphasis on both past and ongoing injustices in Africa. Much stands in the way of achieving equity, and history is full of failed attempts and rhetoric. The scope of obligations includes investing in access to science and healthcare, building localized research capacity and governance, and evolving an ethical and responsive approach to research and development.

Key themes from this discussion:

- African communities deserve investments in anti-malarial technologies, a transparent and informed approach to research, and an apology for colonial exploitation.
- Existing injustices and inequities in technology development require investment in sustainable, independent research institutions in the Global South.
- A human rights-based approach to emerging technologies provides a foundation for developing a comprehensive ethical framework for gene drive development and governance.

Panel 4: Principles to principled action

The final panel discussion in the series explored the role that principles can play in the ethical governance of emerging technologies such as gene drive. Throughout the conversation, panelists discussed both the importance and limitations of principles, as well as different approaches to integrating principles into gene drive research and governance. While highlighting the potential benefits of principles, cautionary guidance included the need for principles that are crafted with broad representation, benefit and reflect the values of relevant stakeholders, and are meaningfully embedded in practice and policy.

Key themes from this discussion:

- The benefits of principles are evident, but operationalizing principles on the ground remains a key challenge.
- Formulated principles will reflect the values and perspectives of those at the table.
- Global principles may conflict with local governance, cultural norms, and needs.

IS THERE A MORAL DIFFERENCE BETWEEN THE NATURAL AND SYNTHETIC?

Summary of Panel 1 Discussion, July 13, 2021

Moderator

Fredros Okumu, Ph.D.
Director of Science
Ifakara Health Institute

Panelists

Matthew Grellette, Ph.D.
Lead, Innovation & Emerging Technologies
Pillar; Assistant Professor, Department of
Philosophy
McMaster University

Kent H. Redford, Ph.D.
Principal
Archipelago Consulting

Ramya M. Rajagopalan, Ph.D.
Associate Director, Training, Evaluation, and
Qualitative Research
University of California, San Diego

Anna Wienhues, Ph.D.
Postdoctoral Researcher, Ethics Research
Institute at the Department of Philosophy
University of Zurich
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The title of this panel discussion, "Is there a moral difference between the natural and the synthetic?" reflects the underlying assumption that there is a moral superiority of the "natural" and a suspicion of the "synthetic." It is at this intersection that gene drive and synthetic biology operate, thus the title provides a specific framing for a conversation aimed at exploring ethical questions concerning the development and deployment of gene drive for use in conservation and public health. As noted in the beginning of the discussion, the dynamic between the artificial and the natural has been a topic of interest since the ancient Greeks separated the "made" from the "born." While technologies continue to shape both social and ecological processes, the panelists discussed whether and which kind of interventions can be morally justified. And although the panelists diligently examined the spectrum of the "natural" vs. "synthetic," they also suggested that this spectrum is insufficient for determining the ethical status of gene drive technologies.

Key Theme 1: The boundaries between the terms "natural" and "synthetic" are ill defined, but the reasoning behind this attempt at categorization highlights important moral considerations.

Throughout the discussion, the panelists examined the ethical implications of the intersection of the natural and synthetic while questioning the seemingly durable boundary between the two. The use of the duality of natural vs. synthetic in regards to the ethical considerations of gene drive was tangled by the fact that each term has a wide breadth of meaning and definition. Anna Wienhues cautioned against using the concept of naturalness without first defining it. The context, definition, and use of this term vary, and not all uses are morally relevant. While she agreed with other panelists that the boundaries between the two concepts are not

entirely distinct, but rather are porous with a gradient between the two extremes, she argued that the over-arching question still matters morally. From an environmental ethicist perspective, the effects on other living beings should be considered when justifying the use of human-made or human-designed technologies. Citing the potential impacts on ecosystems and other forms of life, Wienhues stated, "I think there are good reasons for taking the moral standing of non-humans into account in the context of gene drives." How one considers those impacts will hinge on whether one takes a more anthropocentric perspective or a biocentric perspective.

Matthew Grellette attempted to philosophically contextualize debate around the concept of "natural" by de-scribing how philosophers use the term "essentially contested concepts" for those concepts that lack a sin-gular agreed upon definition and whose meaning is heavily contested. Similarly, Kent Redford referenced the literary scholar Raymond Williams' description of nature/natural as arguably the most complicated word in the English language. The interdependence of humans and other life forms further complicates the categorization of the "natural." Humans already interact with and impact millions of organisms via technologies and societal infrastructures, and the adaptability of those organisms is evidenced by a long history of genetic modification through breeding. Ramya Rajagopalan stated, "All of this makes this line between the natural and the synthetic that much more fuzzy." Because that boundary is blurry, the panelists avoided an in-depth analysis of defini-tions and instead focused on understanding the politics and moral implications of the boundary and what it seeks to separate.

Key Theme 2: Human-designed technologies that rely on biology blur the line between natural and synthetic interventions.

The framing of this panel questioned the moral difference between natural and synthetic approaches to inter-vening in nature; however, bio-technologies do not always fit neatly into one box or the other. According to Anna Wienhues, within an environmental context, humans tend to think of themselves as moral agents armed with a sense of duty to protect—due to both our awareness and the outsized scope of our impact. Wienhues affirmed a moral difference between the natural and the synthetic when it comes to interventions in nature. "We can distinguish between whether something is more or less natural on one side or synthetic/artificial on the other side just as a way of signaling our moral positionality in the world as moral agents who have to make decisions about what we want to do." She described how the natural/synthetic distinction tries to pick up on our moral intuition. She went on to say, "Simply put, we as humans are obviously part of nature, but be-ing part of nature does not justify morally every change we want to do to the environment."

Mathew Grellette challenged the notion that there is an inherent wrongness to gene drive technology due to its "un-naturalness" by pointing out that there are numerous technologies that were initially opposed on the basis of their conflict with nature that are now widely accepted (e.g., automobiles, in-vitro fertilization). Fur-thermore, Kent Redford suggested that the distinction between the natural and synthetic in regards to tech-nology may no longer be relevant or useful in our modern world. In the field of conservation, a wide variety of technologies are already employed that blur the line: "Conservation actively uses fire, fences, shooting of predators, camera traps, drones, environmental DNA, all sorts of technologies, in order to save nature. We are already deeply invested in the use of technology to save nature." He argued that the new question is about the use of genetic tools as a way to try to save nature, which really asks whether we should change nature in order to save it? He proposed the use of counterfactuals in gene drive decision making to ask the question: "Is what will happen to nature worse if we do deploy genetic technologies or worse if we don't?"

Key Theme 3: Focusing on justice, human rights, and humans' responsibility to protect nature helps to reframe questions that too easily trigger debates about the natural vs. the synthetic.

The panelists argue that the natural/synthetic distinction is not the ultimate or even primary moral consider-ation and that to broaden the conversation of ethics in gene drive, a variety of additional considerations need to be examined. In regards to the primary question framing the panel, Anna Wienhues stated, "I don't think that whether something is more or less natural is the ultimate moral consideration that we have to turn to before we ask other questions." She cited the importance of considering ethical questions related to public health, political context, power, and justice. Ramya Rajagopalan emphasized the need to focus on the impacts of technologies on human political and social worlds as well as non-human systems. She posed important

questions regarding a preoccupation with the natural/synthetic divide: "How can we start to decolonize the ways we approach and respond to some of these issues of the boundaries between the natural and the synthetic? . . . For whom might it matter whether there is a moral/philosophical divide between the natural and the synthetic and these sort of panics about tampering with nature? How can we think about the ways in which other priorities might play a larger role in people's lives in terms of their willingness or their ability to mediate nature in ways that enhance human lives." She stressed the importance of understanding differentials in power and equity in the design and deployment of technologies when unpacking these types of ethical questions.

Mathew Grellette articulated the need to expand the conversation to identify moral problems tied to the processes or products of synthetic gene drives. However, he senses that none of these arguments will stand out as particularly compelling in light of the promise gene drive holds to do good in the world. Therefore, he suggested that ". . . our moral attention should also be focused on thinking about how to use this powerful new technology responsibly. That is, we need to think through questions about what counts as an acceptable vs. an unacceptable use case for synthetic gene drives. We need to think about what sorts of institutions are best situated to employ this technology. And what degree of public education or public assent can confer legitimacy upon this technology." Overall, the panelists agreed that each potential application of gene drive will have local and particular ethical considerations to be deliberated on a case by case basis, and developers must be responsive to the needs and concerns of stakeholders.

Key questions

Do humans have a responsibility to preserve nature? If so, which kind of interventions into nature can be morally justified?

Whose interests are served by focusing on the politics of the boundary between the natural and the synthetic?

In what ways do other priorities play a larger role in people's willingness or ability to use biotechnologies?

How can we approach philosophical and ethical considerations of new technologies to advance the discussion around deployment and development?

How can the development of new technologies be responsive to ethical concerns? Whose concerns are relevant? How can design processes be flexible to include feedback and a diversity of expertise?

How do humans represent the interests of nonhumans?

DO JUSTICE AND EQUITY BOLSTER OR HINDER THE CASE FOR GENE DRIVE?

Summary of Panel 2 Discussion, August 10, 2021

Moderator

Sam Weiss Evans, D.Phil.
Senior Research Fellow with the Program on Science, Technology & Society
Harvard University

Panelists

Fred Gould, Ph.D.
University Distinguished Professor, William Neal Reynolds Professor of Agriculture, Co-Director of the Genetic Engineering and Society Center
North Carolina State University

Carolyn Neuhaus, Ph.D.
Research Scholar
The Hastings Center

Anna-Maria Hubert, Ph.D.
Assistant Professor, Faculty of Law
University of Calgary

Carla Saenz, Ph.D.
Regional Bioethics Advisor
Pan American Health Organization

The guiding question framing this panel discussion, "Do justice and equity concerns bolster or hinder the case for gene drive?" reflects the early work undertaken in gene drive research that highlighted ethical concerns and responsibilities. In 2016, the NASEM report *Gene Drives on the Horizon* emphasized attention to stakeholder engagement, justice, and equity in gene drive research—aspects of biotechnology research that have, at times, been historically neglected. Following that report, the 2017 publication of "Principles for Gene Drive Research" in the journal *Science* put forward a set of guiding principles containing a commitment to "include the resources needed to permit robust, inclusive, and culturally appropriate engagement to ensure that the perspectives of those most affected are taken into account" (p. 1136). This discussion forum included panelists who are aiding those efforts to connect research to meaningful, on-the-ground engagement and action related to justice and equity concerns.

Key Theme 1: Because gene drive applications may reduce existing health inequities, researchers have a moral obligation to explore potential applications.

The panelists discussed how established conceptions and principles of justice substantiate the exploration of applications of gene drive to reduce health inequalities, specifically those linked to vector-borne diseases such as malaria. Carolyn Neuhaus outlined different conceptions of justice and how they might frame gene drive decision making related to preventing death and disease: "For example, deaths from malaria are unjust in the sense that they rob people, especially children, all over the world of something they are due: a future or a life. We might say we have a commitment from a substantive conception of justice to reduce morbidity and mortality that is preventable." Anna-Maria Hubert cited international human rights, such as the human

right to science, as a principle that might warrant using gene drive to address global health disparities, but she also highlighted the difficulties in designing and implementing practical approaches to achieve equity in outcomes.

Carla Saenz highlighted the significance of existing global health disparities that undermine equity. She cited the fact that vector-borne illnesses primarily affect poorer countries, and therefore "we have the moral duty to address this huge health disparity." Fred Gould agreed that vector-borne illnesses are diseases of the poor, and for this reason, they are inherently about inequality. These types of inequalities directly impact issues of justice in decision making about gene drive. For example, geographic variability in malaria burden will impact perspectives on how much of an ecological disturbance is justified by employing gene drive to alter malaria-carrying mosquitos. Important questions include: Who decides how much ecological impact is too much, and who does it matter to? Citing the many types of gene drive other than those that could theoretically result in the global extinction of a species, Gould stressed the importance of looking carefully at the details of what is happening on the ground. Preferences for a spatially or temporally restricted gene drive, which avoids the threat of extinction, might seem morally preferable. However, while restricted gene drives are not inherently unjust, the deployment of a "global" gene drive, which does not distinguish between locales, may be more equitable.

Key Theme 2: Geographic disparities in research capacity and governance underlie concerns of justice and equity in gene drive research and development.

Although the panelists agreed that gene drive holds the potential to reduce health inequalities, there was shared concern that gene drive might exacerbate other existing inequities. Disparities exist between the Global North and other countries in both research governance capacities and the processes of development of science and technology. While existing international human rights agreements may serve as vehicles to further priorities of justice and equity within some governance structures, Carla Saenz cautioned that laws designed to provide oversight are just the bedrock. The broader scope encompasses capacities and public trust in science that do not necessarily exist in many countries outside the Global North. Sam Weiss Evans acknowledged, ". . . in other settings, especially low- and middle-income countries, the kind of governance infrastructure [for emerging technologies] more broadly isn't as robust or as developed."

The panelists agreed that focusing on ethical research governance and reducing disparities in research capacity between the Global North and other countries is essential for expanding justice and equity in gene drive research. They questioned how to create these research capacities and how to create channels that effectively share information apart from researchers. While it is necessary to provide clear and transparent information to communities, Carla Saenz noted it is challenging to engage meaningfully in communities that have a baseline of mistrust, a situation that is fueled in part by the gap in research capacities. She added that there is a perception in Latin American countries that gene drive is a foreign technology coming from the North. Therefore, efforts to address health inequalities with new technologies should also include efforts to enhance research and governance capacities.

Key Theme 3: Alternative approaches and forums for practically engaging with questions of justice and equity in gene drive are needed.

The synchronous development of gene drive technologies and the governance system around gene drive necessitates spaces to authentically engage with ethical concerns and responsibilities. Sam Weiss Evans noted that "The technical process of developing is being created at the same time that we're building the spaces and procedures and methods to assess whether it's good and safe and desirable . . . ," and he questioned whether we should use gene drive as a means to create a new ethics governance system. Ethics committees, which can partner locally with affected communities and share knowledge, currently house some of these kinds of ethical conversations. Carla Saenz stressed that it is important to insist on ethics committees and governance entities, but stated that the research ethics committee approach as it stands is not working. Voices are missing from parts of the world, and ethics committees need a louder voice. Anna-Maria Hubert argued for situating gene drive research in environmental governance structures but highlighted that existing laws and mechanisms often fall short.

The panelists imagined creative forums for approaching issues of justice and equity. Fred Gould acknowledged that the avenue of informed consent is not appropriate or sufficient for gene drive technologies and questioned how to measure community consensus. Carla Saenz noted that the global science agenda needs to include a research ethics focus beyond human subjects protections. Carolyn Neuhaus added the complicating factor of how to creatively provide forums for historically marginalized communities: "My worry really comes down to importing principles and ethical and moral commitments from research ethics, which have historically deprioritized, if not ignored, justice and instead looking to other areas of practice like environmental justice and law. . . . How can we have some transformation here, new social structures, new forms of organizing that actually empower other communities in the wake of historical injustice?" There is an opportunity to align the development of alternative forums and their outputs with ongoing research trajectories. Sam Weiss Evans highlighted how this conversation is calling attention to the experimentation going on around different ways of incorporating ethics, equity, and justice concerns and emphasized that those experimentations are just as important as the technical aspects of gene drive.

Key questions

How might gene drive applications both reduce and exacerbate inequalities?

How does the gene drive community create a stronger capacity for attending to questions of justice and equity? What does this look like in practice?

Who benefits most from a particular gene drive application? Who bears the risks? Who is responsible if things go wrong?

How can resources for gene drive research be allocated and distributed equally in a global scientific environment marked by existing disparities in capacity?

What does a just process for gene drive decision making look like?

What role do ethics committees play in gene drive research and development? How do they maintain both independence and relevance?

If the decision is made not to deploy a particular gene drive, how is the cost of "inaction" calculated and reconciled?

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WHO OWES WHAT TO WHOM: WHAT IS THE NATURE AND SCOPE OF RESPONSIBILITIES OF THE VARIOUS ACTORS?

Summary of Panel 3 Discussion, September 14, 2021

Moderator

Jim Lavery, Ph.D.
Conrad N. Hilton Chair in Global Health Ethics, Professor in the Hubert Department of Global Health, and Faculty of the Ethics Center
Emory University

Panelists

David Nderitu, Ph.D.
Lecturer of Philosophy, Department of Philosophy, History and Religious Studies
Egerton University

Nanjira Sambuli
Technology and International Affairs Fellow
Carnegie Endowment for International Peace
Co-Chair
Transform Health Coalition

Fil Randazzo, Ph.D.
Founder and CEO
Leverage Science, LLC

Jantina de Vries, D.Phil
Associate Professor in Bioethics, Department of Medicine
University of Cape Town

Considering the question "Who owes what to whom," the panelists confronted the nature and breadth of obligations bound to the development of gene drive technologies. The scope of obligations spans from investments in anti-malarial technologies, research capacity, and infrastructure to an ethical and responsive approach to research and governance. Notably, this list includes an apology and reparations for both past and ongoing injustices. As the development of gene drive research and governance continues to unfold, much stands in the way of achieving equity, and history is full of failed attempts and rhetoric. This conversation represents an attempt to address past transgressions with humility while building an approach to ethical research and practice guided by dignity, morality, and justice.

Key Theme 1: African communities deserve investments in anti-malarial technologies, a transparent and informed approach to research, and an apology for colonial exploitation.

The nature and scope of researchers' obligations to Africa are wide and varied. Citing evidence that colonial activities in Africa have increased the spread of malaria, David Nderitu stated that western countries, particularly the colonial countries, owe a debt to Africa and have the responsibility to invest in anti-malarial technologies. However, he stressed the need for international organizations funding research and healthcare to pursue local needs informed by local stakeholders.

Within local communities impacted by research activities, researchers have an obligation to communicate clearly and effectively. This includes explaining scientific concepts that may lack equivalent terms in the local languages and addressing technical questions, concerns, and perceptions of risk that are informed by

past experiences. Researchers may also need to provide rationale for their site selection process to create transparency and open communication. David Nderitu and Fil Randazzo both addressed the issue of misinformation in research and its impacts. Randazzo stated that Africa is owed the freedom from misinformation, which runs rampant around new technologies. And Nderitu stressed the need to respect the experiences people have lived through and the misinformation they've been exposed to that might inform their willingness to participate or not.

Consent for research is a special category of responsible communication. Jantina de Vries noted that the freedom to refuse to participate in research is important, and Nanjira Sambuli reflected on the power dynamics at play when a researcher uses incentives, such as cash or access to much-needed healthcare, which can impact an individual's ability to opt out of research activities. She highlighted the need for an ethical approach to consent that goes beyond lip service and "tick-the-box" consent forms that fail to adequately inform research participants.

Nanjira Sambuli broadened the scope of responsibility: "Western researchers and institutions owe what I'll call the African subject, since that is what she is usually referred to, they're owed first and foremost an apology for years of treating her as a guinea pig and as a lesser being not deserving of dignity in the experiments that have been conducted over centuries." She stated that Africans are owed reparations for both past and ongoing atrocities and reminded the audience that the past informs the present: "And many of these experiments still inform how science research is conducted, including in genetics . . . and we really do need to figure out how we put it back and stop it and make sure that the future is not always tainted by this." Jim Lavery agreed that the role of apology as a form of acknowledgement and humility is extremely important and often neglected.

Key Theme 2: Existing injustices and inequities in technology development require investment in sustainable, independent research institutions in the Global South.

Developing and deploying new technologies, including gene drive, can contribute to injustice, exclusion, and inequality when less developed countries lack the capacity and infrastructure to benefit. Nanjira Sambuli addressed what African governments, policy makers, and their supporters in the development community owe African communities: "an investment in sustainable, independent institutions that can house indigenous and contemporary knowledge by homegrown scholars to contribute to gene drive research." According to David Nderitu, African governments have a responsibility to collaborate with local scientists and build research capacity within African countries in order to align gene drive development with local systems, institutions, and researchers. Jantina de Vries emphasized the need to empower young African scholars and scientists to shape African perspectives on and innovations in science on their own terms, not in relation to powers elsewhere. Nderitu noted that international funders and collaborators can help establish academic programs that ensure progress is sustainable, and local governments need to fund and ensure regulations that institutionalize these activities and continue progress.

Local governments have a duty to support efforts to eradicate malaria, including setting priorities, effectively allocating resources, contributing to research, and funding adequate healthcare. In regards to the governance of new technologies aimed at improving health, such as gene drive, African governments have an obligation to set regulations and create safety systems. Fil Randazzo described how the Western research community owes their support to the innovation happening on behalf of African scientists as those scientists lead, try, and test new malaria interventions. He added that Africans deserve freedom from distant political battles in order to prevent malaria deaths and disease and that the Western world needs to keep their philosophical battles over technology distinct from Africans' decisions about how to and whether to deploy technologies. Randazzo emphasized the need for robust funding that includes community engagement, testing all aspects of the technology in terms of safety and efficacy, and building local research capacity. He referenced the work that was done to build capacity on the ground by Target Malaria in Burkina Faso, ahead of the maturity of gene drive technology. Funding for lab infrastructure, community engagement, and technical development built a base for the scientific progress to evolve. Jim Lavery added that "We all know that there are capacity issues, but all of us here also know that there is no lack of talent and capability in the [African] Continent."

Key Theme 3: A human rights-based approach to emerging technologies provides a foundation for developing a comprehensive ethical framework for gene drive development and governance.

Among the panelists, there was broad recognition of the need to support more equitable and inclusive technology development and innovation while ensuring everyone has access to the benefits of science. In order to build research capacity and ensure universal access to the benefits of emerging technologies, the research community owes the world a more robust and egalitarian approach to ethics. Nanjina Sambuli stated that the African Charter on Human and Peoples' Rights can inform and guide this ethics work. Jantina de Vries, citing the Universal Declaration of Human Rights recognition of the right of everyone to "share in scientific advancement and its benefits" (Article 27(2)), asserted that all people are entitled to access the benefits of science and its applications in order to live a dignified life. According to de Vries, achieving equity means that the instruments and tools of science benefit all equally, and the duty of ensuring equity accrues to all.

The panelists also acknowledged that much stands in the way of achieving equity in science, and history is full of failed attempts and rhetoric. Jantina de Vries highlighted the need to acknowledge the impacts of power dynamics and systemic biases that currently guide technological development in science. Nanjira Sambuli emphasized the importance of bringing complexity to these conversations, rather than simplifying them; of bringing nuance to the discourse. And she noted that there is restorative and reparative work needed to approach what has already become the norm. She described the need for a research ethics that is guided by dignity and morality and recognizes each African research participant "as an actor and an agent with indigenous and contemporary insights that should be accommodated in every step of the research process from deliberation to decision making to deployment and any other intermediary stage. It's an ethics that needs to discenter the non-African as a savior or the one who knows what's best for the African in her environment. This is an ethics of humility and praxis and not just a bunch of signaling."

Key questions

How can the research community provide more transparent rationale for where and why scientific research is located in some places and not others? How can they make good on the obligation of procedural and substantive fairness?

How can researchers account for power dynamics to ensure either individuals, communities, or countries are in positions to opt out of participation in technologies like gene drive?

Can we scale up individual consent models to account for the need for community consent for gene drive field trials, or do we need to rethink the ethics paradigm from the ground up?

How do we ensure equitable distribution of technology development across the world through upstream decisions about how and where to invest in science?

How can international funders and research collaborators remove barriers and better support aspiring African scholars and scientists?

Resources

Organization of African Unity (OAU), African Charter on Human and Peoples' Rights ("Banjul Charter"), 27 June 1981, CAB/LEG/67/3 rev. 5, 21 I.L.M. 58 (1982), available at https://www.refworld.org/docid/3ae6b3630.html [accessed 27 May 2022].

UN General Assembly. Universal Declaration of Human Rights. United Nations. (1948). http://www.un.org/en/universal-declaration-human-rights/.

FROM PRINCIPLES TO PRINCIPLED ACTION: WHAT ETHICAL PRINCIPLES OUGHT TO GOVERN GENE DRIVE RESEARCH?

Summary of Panel 4 Discussion, October 12, 2021

Moderator

Katherine Littler
Co-lead, Global Health Ethics and Governance Unit
World Health Organization (WHO)

Panelists

Alta Charo, J.D.
Emerita Professor of Law and Bioethics
University of Wisconsin

Abha Saxena, M.D.
Bioethics Advisor
Independent

Aaron Roberts, M.A.
Graduate Research Assistant and Ph.D. Candidate
McMaster University

Nienke de Graeff, M.A., M.D.
Ph.D. candidate
University Medical Center Utrecht

The title of this discussion, "From principles to principled action: What ethical principles ought to govern gene drive research?" signifies that there is a vital role for principles to play in the ethical governance of emerging technologies such as gene drive. Principles can support efforts that aim to find the balance between the expected benefits and potential harms or unintended consequences of new technologies. Previous and ongoing efforts to craft relevant, meaningful principles include the 2017 *Science* publication, "Principles for Gene Drive Research"; the 2020 WHO guidance, "Ethics and Vector-borne Diseases"; and the 2021 *CRISPR Journal* article, "A Code of Ethics for Gene Drive Research." However, it is one thing to develop principles, and it is another to make them meaningful and embedded in practice and policy. Throughout the conversation, panelists discussed both the importance and limitations of principles for gene drive, as well as different approaches to integrating principles into gene drive research and governance.

Key Theme 1: The benefits of principles are evident, but operationalizing principles on the ground remains a key challenge.

The panelists emphasized the value of principles in gene drive research, but with cautionary guidance. Alta Charo described how the adoption of principles can build trust for an emerging technology, as the exposition of principles creates transparency and accountability. She described how principles help to provide an understanding of the technologies being developed and the process of development and thereby make it easier for people to both accept expert judgment, as well as hold those experts accountable. "The way to develop some degree of trust on the part of a community in delegating some of its decision making authority and policy making authority to others, whether elected officials, or regulatory agencies, or professional societies . . . is by adopting certain principles that will allow the community to feel like they know what is going on." Aaron

Roberts agreed that principles have a useful role to play, but he highlighted the importance of thoughtfully grounding principles in values: "Principles can guide us. They can be very useful, but without making explicit the values that are guiding our use of the principle, without orienting our use of the principle through explicit values and having a firm understanding of the values we are prioritizing, we can start to talk past each other as we use principles, since one group may be filing in all of those value variables in a very different way from another."

Nienke de Graeff also underlined both the importance of stipulating ethical principles to guide gene drive research and the pitfalls of relying on ethical principles alone. She described how "it is relevant and important to formulate ethical principles as these can firstly provide a common framework of justification that can be used to guide and evaluate gene drive research, and can secondly provide a set of principles that can be applied across nations, disciplines, and legislations." However, she emphasized the general nature of principles and the challenge of using them as precise guides to action. She added, ". . . to really live up to these promises, it's also necessary to move from these general overarching principles to concrete moral obligations that stipulate which actions should be conducted or avoided and where, when, how, why, and by whom." Additionally, she noted that agreement on broad principles may obfuscate underlying disagreements or ambiguities. She used community engagement as an example: while there is broad agreement on the importance of engagement as an essential principle, there are divergent views on what that entails.

Key Theme 2: Formulated principles will reflect the values and perspectives of those at the table.

Although principles are intended to be applied across communities, their formulation will reflect the values and perspectives of the people with a voice in developing them. Abha Saxena stated that we need principles that work for everyone. Using gene drive technology as an example, she described how different stakeholders have different uses for principles. Scientists in the developed world use principles to guide them in developing a helpful technology without adverse ecological effects. Scientists in developing countries need principles to improve their standing in the scientific world and ensure their contributions are acknowledged. Impacted community participants want principles to protect their health, well-being, and ecology. Governments use principles to ensure populations have access to new technologies. Highlighting these diverse viewpoints, Saxena questioned whose viewpoint will count and expressed concern that voices are missing from the table. ". . . so far, the principles and . . . most of the discussions on principles, moral considerations, codes of conduct, have been led by people in the North, by people in European and American universities and organizations. And they have not involved so much the scholars, the publics, and the regulators of the less developed countries. And therefore, we don't hear all the voices that we ought to be hearing in the debate."

The panelists agreed on the importance of having representatives from historically underrepresented groups at the table when principles are being established. They noted that different stakeholders will have different perceptions and tolerances of risk for various interventions, such as gene drive for malaria control. Alta Charo noted that ". . . things that might not have been acceptable in certain countries in the North will be tolerated in the South because you have such a strong need for moving forward the health research on, for example, a locally, financially, and logistically manageable therapeutic intervention." Aaron Roberts cautioned against the adoption of principles that would prevent individual countries from doing their own risk analysis on whether a technology would be worthwhile to try in their space. Using malaria as an example and referencing again their use of the precautionary principle, he noted that "Europe does not suffer from malaria. And so the thought of introducing genetically modified organisms which would spread through the environment and change ecologies seems like a needless risk from that perspective. It seems somewhat myopic though to try and impose those sensitivities and that risk analysis on the entire world. And not for a specific product but for an entire field of research and all the myriad products that might come from that." Nienke de Graeff stated that the principles are being put forth primarily by scientists and academics from the Global North, and that this is something that should trouble us. She acknowledged that this bias was also noted in the *Science* publication of gene drive principles (Emerson, et al., 2017). Charo, reflecting on her previous work on a WHO genome editing committee, noted how that panel had a lot of representation from non-Northern countries and how that affected conversations around usability. She described how having broader representation at the earlier stages of the conversation impacted activities down the road in concrete ways.

Key Theme 3: Global principles may conflict with local governance, cultural norms, and needs.

Like gene drive applications, principles transcend political boundaries and extend across both nations and disciplines. Although principles are intended to be universally applied, the panelists acknowledged some of the challenges to implementing global directives at the local level. Abha Saxena noted that in regards to gene drive, individual countries and governments may not have a voice or role in establishing the global principles and rules by which they are governed. How might a principle approved by the global community interact with local policy and legislation? She addressed the complexity that arises when global principles conflict with local principles and cultural norms. Relatedly, Katherine Littler wondered how prescriptive some of these global instruments should be when applied locally. Aaron Roberts addressed this entanglement and questioned how to address conflicting principles. For example, if Ghanian principles or decision making processes conflict with global principles or ethics that guide the Global North research institutions, which principles should be prioritized in actions on the ground? The panelists made reference to ethical analysis as a tool to use more often to identify the relevant issues and principles.

Referencing the 2021 plenary vote by the European Parliament, which used the precautionary principle to put a moratorium on gene drive research that would lead to the release of a gene drive organism into the environment, Aaron Roberts described how the European Union (EU) political agendas were having an outsized weight on the conversation about the use of gene drives globally. He addressed how the EU's decision might impose restrictions on the rest of the world, including areas with a high malaria burden that stand to benefit from gene drive products, such as altered mosquitoes designed to stop malaria transmission. In this case, the precautionary principle is not well articulated and lacks a mechanism to deal with a risk-risk comparison, such as the difference in malaria risk between the EU and countries in the Global South. Roberts continued, "All this to say that the precautionary principle, it works differently at the different levels you might want to apply it. And if you want to apply it globally in a way that would prevent a more local assessment, that seems inappropriate, unjust, and reckless."

Key questions

What are principles meant to achieve? Who are these principles meant to serve?

What actions and responsibilities follow from principles?

How do we ensure we have the right people at the table when formulating principles? How can these processes empower those who have been harmed historically?

When articulating a principle, such as the precautionary principle, what constitutes relevant, scientific evidence? How do we account for people's various attitudes towards risk and uncertainty?

How prescriptive are global instruments? How do global regulations translate to the local level?

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