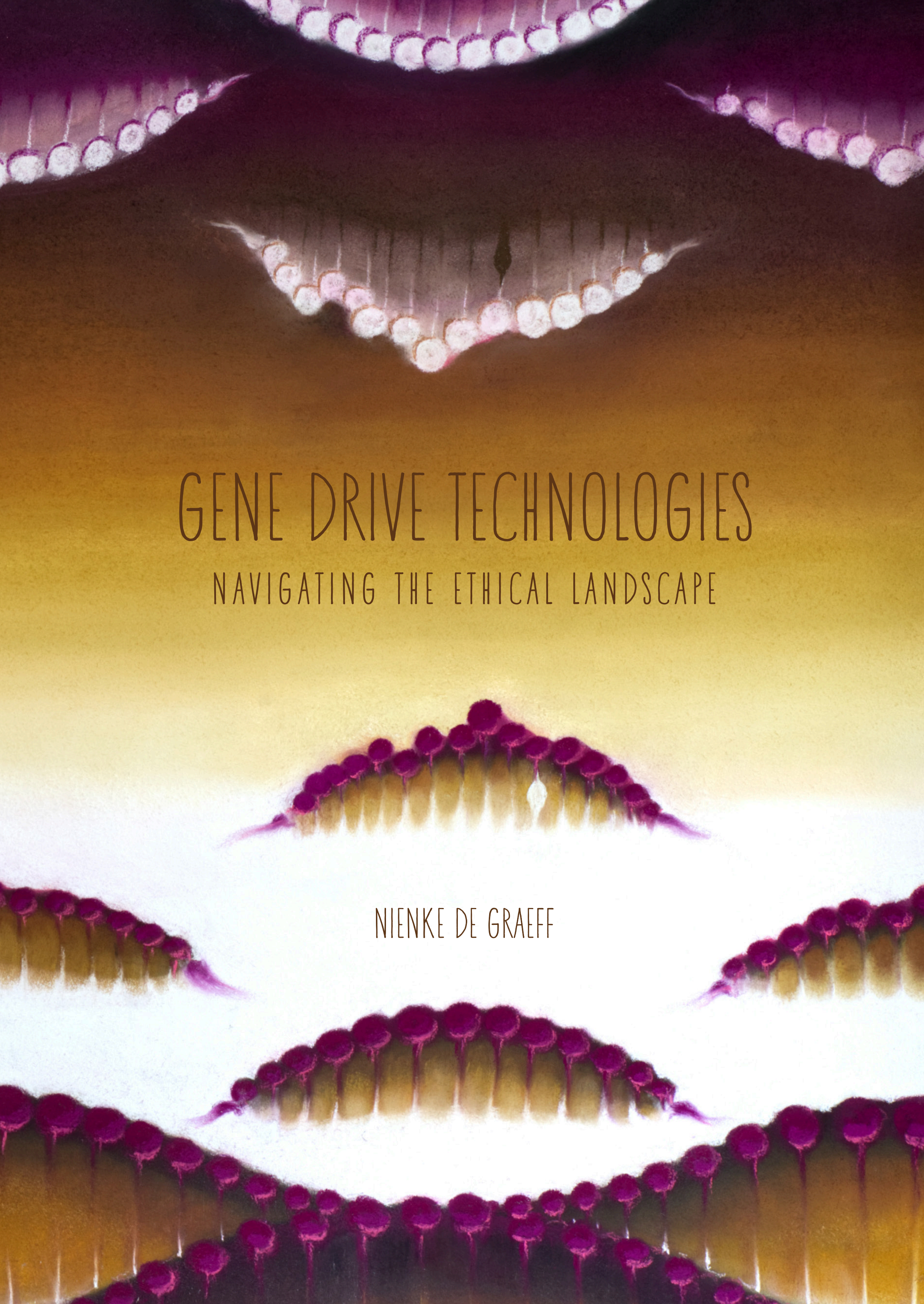

GENE DRIVE TECHNOLOGIES

NAVIGATING THE ETHICAL LANDSCAPE

NIENKE DE GRAEFF

Gene drive technologies

Navigating the ethical landscape

Nienke de Graeff

Gene drive technologies: Navigating the ethical landscape.
PhD thesis, Utrecht University, the Netherlands.

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Gene drive technologies

Navigating the ethical landscape

Gene drive technologieën

Navigeren door het ethische landschap

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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GENERAL INTRODUCTION

In the context of the rapid developments in genetic modification in the past decades, it is easy to forget that the Austrian monk Gregor Mendel presented his insights on the mechanisms of biological heredity less than two centuries ago (1). By breeding and crossing tens of thousands of pea plants and studying the resulting offspring, Mendel deduced how traits were inherited (2). Amongst other things, his observations demonstrated that sexually reproducing organisms have a 50% chance of passing on a particular genetic element to their offspring. As a result of this so-called 'Mendelian inheritance', the frequency of a particular genetic element either stays constant or gradually decreases over time, depending on its fitness costs (see Figure 1).

Later scientific studies showed that there are also genetic elements that are not passed down according to these conventional rules of inheritance. Indeed, some genetic elements bias inheritance in their favor, such that they are spread to more than 50% of offspring. These genes are said to 'drive': they show greater than Mendelian or 'super-Mendelian' inheritance patterns (3) (see Figure 1). Gene drives – like the so-called 'transposable element P' that was discovered in fruit flies and became the first gene drive to be extensively studied (4,5) – can rapidly increase the frequency of a particular gene across generations even if it does not provide a fitness advantage to the organism (3,6).

Figure 1. Mendelian inheritance and gene drive inheritance

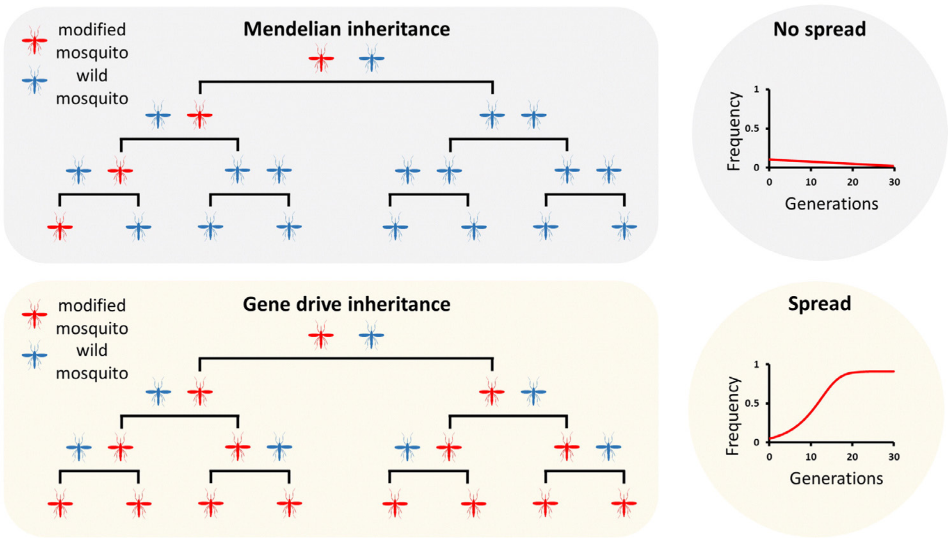

Figure reproduced from Hammond & Galizi (5)*; no changes made; CC BY.*

The discovery of these 'natural' gene drives[1] sparked the interests of scientists who were keen to decipher their underlying molecular mechanisms, but also of those who envisioned their potential practical implications. Evolutionary geneticist Austin Burt realized this potential early on; if it was possible to develop gene drive technologies (GDTs) that spread specific traits, he reasoned, these could potentially be used as tools to control populations of non-human animals that are harmful to humans (7). Whereas genetic modification (GM) technologies may be used to edit a genetic element in individual organisms, GDTs could be used to spread this edited element across a population or even a species[2].

In recent years, this possibility has come within closer reach (8–10). If successful, GDTs could be used to tackle impactful problems that humans have thus far not been able to resolve through other means. GDTs could, for example, be used to foster public health by targeting organisms that carry infectious diseases that affect humans, such as malaria, dengue, or Lyme disease. They could also be used for ecosystem conservation, either by targeting organisms that carry infectious diseases that threaten the survival of other species, or by targeting invasive alien species[3] that threaten native species and biodiversity. Furthermore, they could be deployed in agriculture to target organisms that damage or infect cultivated crops or to reduce or eliminate weeds that compete with these crops (8).

At the same time, the prospect of using GDTs to edit organisms in our shared environment raises important ethical questions and concerns. Amongst others, these ethical issues relate to the potential risks of GDTs for humans, non-human animals and the environment, the position that humans should have in nature, and how the development and potential deployment of GDTs can be guided responsibly. The proactive identification and evaluation of these and other ethical issues related to GDTs is essential to facilitate their responsible development and governance. Therefore, the aim of this PhD thesis is to identify the ethical challenges of GDTs and to evaluate how GDTs can be developed and governed[4] in an ethically responsible manner.

1 Scientists frequently refer to gene drives that are found in the wild as 'natural' gene drives, in contrast to gene drives that are created using recombinant DNA techniques in the laboratory, so-called synthetic gene drives or gene drive technologies (GDT) (88). For more elaborate reflections on the conceptual and normative complexity of the terms nature and natural(ness) in the literature on genetic modification, see De Graeff N, Buijsen MAJM & Bredenoord AL (2022). On the Nature of Nature: A study on the use and meaning of nature and (un)naturalness in the literature on genetic modification. The Hague: Commissie Genetische Modificatie (COGEM), rapport nr. CGM-2022-01.

2 It is important to note that GDTs can only be used in sexually reproducing species and would only be capable of producing rapid and significant population-wide effects in organisms with a short generation time, such as insects and small rodents (11). In organisms with a long generation time, such as humans, it would take centuries to produce such effects (90).

3 As is discussed on page 11, the term 'invasive alien species' is generally used to refer to non-native species that enter a particular ecosystem and threaten native species and biodiversity within that ecosystem. There has been substantive debate on what exactly constitutes an invasive species (see for example (91)). The same goes for the term 'pest' (92).

4 Technology governance may be defined as the "process of exercising political, economic and administrative authority in the development, diffusion and operation of technology in societies" (93). Governance thus encompasses a broad range of mechanisms to steer technology development and deployment (76,93).

Background

Gene drive technologies: the state of the art

While various types of GDTs using different molecular mechanisms have been proposed (8,11), the emergence of CRISPR-Cas9[5] in 2012 has led to particular advancements in the field. It is important to note that research is conducted on GDTs with different dynamics and levels of intended persistence in the environment. So-called 'nonlocalized', 'self-sustaining' or 'self-propagating' gene drives are designed to spread across a target population from low initial frequencies (5,12,13). So-called 'localized' gene drives, in contrast, are intended to spread in a manner that is spatially and/or temporally limited due to genetic or molecular confinement (5,13). Within the latter group, two types of GDTs can be distinguished: localized, 'high threshold' drives and 'self-limiting' drives. High threshold drives need a high starting frequency to spread across a target population. Consequently, these GDTs are envisioned to be restrained geographically since spread to a neighboring, nontarget population would likely start at a low initial frequency that is under this high threshold (12,13). Self-limiting gene drives are intended to be temporally as well as spatially limited: they are designed to be able to drive only for a limited amount of time (12,13). This may for instance be established by using a GDT design based on several independent genetic elements, with each element driving the next. Once the bottom element is lost from the population, the successive elements cease driving and are in time also lost from the population (12,14).

Roughly speaking, GDTs have been proposed for two main strategies of population control. In the first strategy, population *suppression*, the spread of the genetic element in question causes the number of organisms in a population to decrease, for example by reducing the fertility of a species or by biasing sex ratios (15). In the second strategy, population *replacement*, the spread of the genetic element changes the genotype of the organisms, for example making the organism resistant to a particular disease which it normally transmits to humans (16) (see Figure 2).

5 CRISPR (Clustered Regularly Interspaced Palindromic Repeats)-Cas9 (CRISPR-associated protein 9) is a GM technology that is considered more precise and versatile than previous genetic modification technologies (94). CRISPR-Cas9 is one of the molecular mechanisms that can be used to create GDTs.

Figure 2. Population suppression and population replacement

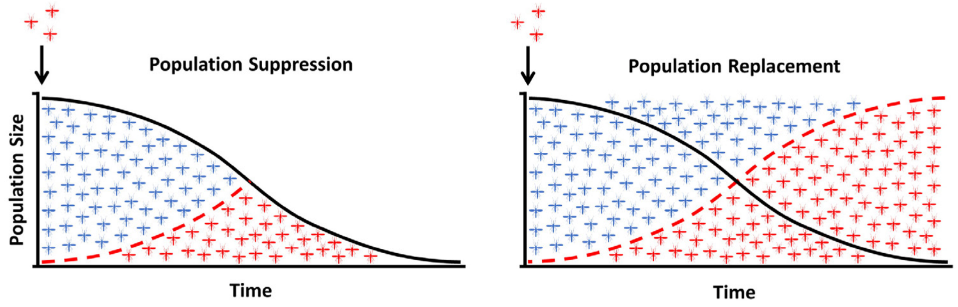

Figure reproduced from Hammond & Galizi (5)*; no changes made; CC BY. The wild-type mosquitoes are represented in blue, the gene drive mosquitoes in red. The solid black line represents the size of the wild-type mosquito population, and the red dotted line represents the size of the transgenic gene drive mosquito population.*

So far, proof-of-concept GDTs have been developed in yeast (17), the plant species *Arabidopsis* (18), the fruit fly species *Drosophila melanogaster* (19,20) and *Drosophila suzukii* (21), the mosquito species *Anopheles stephensi* (22)*, Anopheles gambiae* (15,23,24) and *Aedes aegypti* (25), and mice (26). In *Anopheles gambiae,* suppression GDTs were also tested in large indoor cages that aimed to partially mimic ecological conditions in the wild (27). These laboratory and cage studies are accompanied by mathematical analyses and predictive modeling to inform the environmental risk assessment of gene drive organisms (28–30). In recent years, the prospect of moving from laboratory and cage experiments and predictive modeling to field trials with gene drive organisms in the coming five to ten years has been raised (13,31,32). For potential field trials with gene drive mosquitoes, the reports by the US National Academies for Sciences, Engineering and Medicine (NASEM), the African Union (AU) and the New Partnership for Africa's Development (NEPAD) on gene drives as well as the World Health Organization (WHO) guidelines for testing GM mosquitoes advocate a phased testing approach. In such an approach, GDTs would be investigated in a step-wise manner: first in laboratory studies, then in small-scale, confined field experiments, followed by open small-scale releases and finally large-scale field releases (8,33,34).

Thus far, most basic research and aspirations for potential applications of GDTs are focused on controlling vector-borne diseases such as malaria. A non-profit organization called 'Target Malaria' aims to reduce the population of malaria-transmitting mosquitoes in sub-Saharan Africa by developing and deploying GDTs in African countries such as Burkina Faso, Mali and Uganda (32,35). Until now, the only field studies that have been conducted by Target Malaria involved the release of non-gene drive GM sterile male mosquitoes[6] (36). They estimate the potential environmental

6 Different novel, non-gene drive approaches to vector control have been field-tested by various other organizations and companies, such as Oxitec's OX513A genetically modified mosquitoes, and EliminateDengue's and MosquitoMate's *Wolbachia*-infected mosquitoes. See e.g. Schairer *et al.* (2021) (95) and Singh (2019) (96) for reflections on these field trials.

release of GDT mosquitoes, representing the ultimate phase of the research, to be "years away" (p. 9) (37). Next to Target Malaria, a non-profit organization called Island Conservation studies the possibility of using GDTs to control invasive species in the 'Genetic Biocontrol of Invasive Rodents (GBIRd)' program, a partnership between different universities, governments, and non-governmental organizations (38,39).

Controlling vector-borne disease, invasive species, and agricultural pests

GDTs are proposed as a potential way to tackle various challenges in the field of public health, conservation, and agriculture. Arguably, the most pressing of these problems are vector-borne diseases such as malaria, dengue, and zika. Despite widespread and worldwide efforts to eliminate these diseases, they continue to have an enormous negative impact on public health. While antimalarial medication and preventive measures such as bed nets and insecticides have led to a decline in morbidity and mortality over the years, further progress in targeting malaria is hampered by a lack of financing and the emergence of drug and insecticide resistance (40). Moreover, even optimal application of these interventions may not be sufficient to eliminate the disease in highly affected regions (40). In 2020, malaria alone affected an estimated 241 million individuals, with a fatal outcome in 627.000 cases (41). Additionally, vector-borne diseases disproportionately affect children, the elderly, and people living in poverty (41,42). The morbidity and mortality of these diseases, coupled with the inefficiency of conventional strategies, has led authors to argue that there are prima facie reasons to go forward with research and/or implementation of innovative strategies to control malaria, such as GDTs (22,43–45). In 2020, the African Union Development Agency – NEPAD (AUDA-NEPAD) for instance outlined commitment to assist "African Union Member States [in building] sound regulatory capacities to safely harness gene drive opportunities for malaria elimination" (p. 2) and the African Union's High-Level Panel on Emerging Technologies identified GDTs as one of three 'priority technologies' for the years to come (46).

Like vector-borne diseases, invasive species and agricultural pests remain a challenge. Invasive alien species – non-native species that are intentionally or unintentionally moved beyond the limits of their native geographic range by human activities, and subsequently threaten native species within other geographical regions – are considered a main cause of animal extinctions and biodiversity decline (47). Agricultural pests, likewise, continue to affect crop yields due to disease transmission, pathogenicity, resource competition and pesticide resistance (48). As a result, these pests may threaten agricultural productivity and food safety, and cause significant economic losses (12). Conventional strategies such as pesticides, trapping, hunting and habitat removal may be insufficiently successful to target invasive alien species and agricultural pests, as well as expensive, labor-intensive and/or harmful to the environment. Therefore, various authors have argued there are also prima facie reasons to explore GDTs in these contexts (12,48–50).

Ethical issues related to gene drive technologies

The development and governance of GDTs raise a range of ethical questions and concerns that warrant proactive ethical evaluation. In the past years, several papers have explored various ethical aspects related to GDTs (45,51–53). In these unfolding discussions, particular aspects of GDTs stand out. In contrast to many GM technologies, GDTs are intended to elicit the progressive spread of a particular genetic element, potentially in a self-sustaining or self-propagating way. Moreover, GDTs are intended for potential use in wild species, whereas GM technologies are predominantly intended for deployment in cultivated crops and laboratory and farm animals. These aspects underline the importance of evaluating various ethical questions and concerns (54).

First, a central ethical matter concerns the uncertainty related to GDTs and their potential risks for people, animals, and the environment. Discussion in the academic literature has focused on biosafety and biosecurity issues[7] related to GDT research, ways to safeguard experiments in the laboratory, and risk assessment of gene drive organisms (8,55–57). The risks of GDTs are context dependent and related to the organism and ecosystems in which they would be deployed, as well as the strategy and design in question (12). Amongst others, potential risks of a GDT field trial could include non-target effects (i.e. harm to other species that were not intended to be affected), 'empty niche' effects (i.e. the risk that a suppressed species could be replaced by another, similarly or more harmful species), evolutionary counter pressures (that could allow malarial parasites to be carried by other species or to become more virulent), and ecological imbalances resulting from the intended or unintended suppression of a species (8). Since laboratory and cage experiments can never fully represent an ecosystem outside the laboratory, there is inherent uncertainty about the outcome of field trials with gene drive organisms. An environmental release poses risks (54,58,59), raising questions about whether and if so, under what conditions such a 'leap of faith' could be justified.

Second, the intended use of GDTs in wild populations raises questions regarding whether and if so, under what conditions humans should intervene in nature in this way. Various publications on GDTs underline their (anticipated) ability to alter our environment in no uncertain terms. Different authors stress that GDTs "represent an entirely new approach to ecological engineering" (p. 2) (60), constitute "a significant increase in the power of humanity (..) to intentionally engineer ecological systems and communities" (p. 39) (61) and would allow us to "sculpt evolution" by "redesigning creatures to better meet our needs by forcing biased genetic inheritance" (62). The Sustainability Council

7 Biosafety refers to measures taken to reduce exposure to and release of biological materials and preventing their accidental release, whereas biosecurity refers to measures taken to prevent their illicit use and deliberate release for malicious purposes (14).

of New Zealand similarly argues that GDTs precipitate "a constitutional moment" as they "radically [exceed] the existing boundaries of human power over nature" and represent a "technological power surge that [propels] society to examine its relationship to, and interdependence with, other species in the biological community and the biosphere" (p. 16) (63). The foundational report on GDTs by the NASEM similarly stresses that the "perspectives on the place of human beings in ecosystems and their larger relationship to nature – and their impact on and manipulation of ecosystems – have an important role in the emerging debate about gene drives" (p. 18) (8). Similarly, some authors mention concerns of this sort in a broader context. Christopher Preston argues that GDTs and other technological advances in synthetic biology, nanotechnology, and climate engineering, have propelled us into what he calls the 'Synthetic Age' (64). This 'Synthetic Age' is characterized by mankind's increasing power to shape and design the world, raising questions about whether this is desirable, as well as about who should be entrusted with making such choices for our future.

Third, the progressive spread of GDTs has important implications for the governance of and decision-making about GDTs. In recent years, different policies have been outlined to govern GDTs in the past years, ranging from voluntary consensus statements to (inter)national regulation (9,13,43,65–69). It has also been proposed that research on GDTs could be governed through so-called 'ethical licensing' in which patents are used to achieve private governance by controlling who is allowed to get a license (70,71). GDT researcher Kevin Esvelt, for instance, proposed to use patents to prevent other researchers from using GDTs without first disclosing their research plans or conducting research without particular safety procedures in place (70,71). Moreover, Monsanto has purchased a license to CRISPR patents from the Broad Institute of the Massachusetts Institute for Technology (MIT) and Harvard that came with the proviso that Monsanto could not develop a gene drive (71). Since the spread of gene drive organisms will not be limited by the borders of particular communities or nation-states (8,72), GDTs moreover invoke questions about how the interests of different communities, stakeholders, and publics should be balanced, who should be involved in related governance and decision-making, and in what way (8,73–76). In discussions on these matters, the role that communities should play has received particular attention (73,77).

All in all, these and other issues warrant careful reflection and ethical consideration. At the start of this PhD thesis, few articles had been published on the ethics of GDTs. As will be specified in the next section, this thesis aimed to contribute to this emerging ethical debate on GDTs by both systematically identifying the ethical implications of GDTs and evaluating them.

Central aim and research questions

Central aim

The central aim of this PhD thesis is to identify the ethical challenges of GDTs and to evaluate how GDTs can be developed and governed in an ethically responsible manner.

Research questions

1. What are the ethical challenges of GDTs?
2. How can GDTs be developed and governed in an ethically responsible manner?

Research approach

Ethics parallel research

As the previous sections have demonstrated, GDTs have large potential, but also invoke ethical questions and concerns. The questions and concerns that GDTs raise and expose resemble so-called 'wicked problems': problems that concern various disciplines and stakeholders and that invoke discussion and disagreement regarding what the problem is as well as what the desired solutions should be (78). Consequently, GDTs also lead to public and academic discussions, with different organizations and stakeholders taking different stances regarding whether GDTs should be deployed, and if so, under which conditions. To disentangle these problems and discussions, this PhD thesis employs so-called 'ethics parallel research'. In ethics parallel research, the aim is to provide ethical guidance of technological development in an early stage, proactively or parallel to development of the technology itself (79). As GDTs are in their early stages of development, with proof-of-concept GDTs having been developed in various organisms in recent years, now is an excellent time to conduct ethics parallel research as its findings can still proactively guide the development and governance of these technologies.

To do so in a meaningful way, it is essential to collaborate with and learn from the researchers that develop these technologies as well as from other experts and stakeholders with relevant knowledge and perspectives (79). Doing so prevents armchair philosophy, ensures that ethics research is well-informed, and enables co-production in which different experts and stakeholders work together to facilitate responsible research and innovation. In the research conducted in this PhD thesis, this was facilitated in several ways. First, the research was part of a larger NWO-funded project on novel genome editing systems with consortium members and user committee members from the life sciences, bioethics, and various non-governmental and academic organizations. Second, a part of this research presented in this PhD thesis was conducted during a research visit to the genetics department of Harvard Medical School in Boston. This provided an excellent opportunity to engage with life science and ethics researchers at Harvard University and MIT who play a prominent role in GDT research. Third, this dissertation includes empirical ethics research in which experts from different relevant disciplines provided their moral views on GDT development and governance in a qualitative interview study. Qualitative interviews are a valuable method to identify, better understand, and juxtapose people's moral views; they can improve the understanding of ethical implications of a technology by providing insights into how interviewees view and weigh different ethical aspects (80).

Wide Reflective Equilibrium

At the same time, the inclusion of empirical ethics research also raises questions about how the different arguments, stances and moral views that are identified in the conducted qualitative interviews eventually influence the normative conclusions that are drawn and defended in this PhD thesis. Indeed, a priori reliance on the intuitions or moral judgements identified in empirical ethics research may lead to prejudice or bias. At the same time, a priori reliance on theoretical moral principles may amount to armchair philosophy in which important moral considerations may be missed, as was argued in the previous section. To prevent this, insights from empirical research and ethical theory should mutually influence each other (81). Moreover, different arguments, stances and views should be evaluated based on their coherence, validity and persuasiveness (79).

Wide Reflective Equilibrium (WRE) is a method for moral reasoning that is particularly well-suited to integrate the insights from empirical research and ethical theory (81). WRE was originally developed by John Rawls (82,83) that has been further developed and applied by many other philosophers, such as Norman Daniels (84). This method attempts to produce coherence between considered moral judgements, applicable moral principles, and relevant background theories by going back and forth between them. In this process, these moral judgements, principles, and theories are analyzed systematically and critically and adjusted where needed to reach a coherent moral view. The resulting outcome, which is also called a reflective equilibrium, is seen as a 'provisional fixed point': a provisional conclusion that remains open and subject to subsequent refinement (84). In this sense, the normative conclusions defended in this PhD thesis should thus most definitely be seen as an invitation for further normative reflection and discussion.

Structure of this PhD thesis

Part I: The ethical landscape – identifying the ethical challenges of GDTs

The first part of this thesis investigates the 'ethical landscape' of GDTs by identifying the ethical challenges of GDTs. Discussions on new and emerging technologies often feature similar patterns of moral argumentation (85). For this reason, it is relevant to the discussion on GDTs to explore what can be learnt from discussions on genome editing more generally. With this aim, **Chapter 2** presents the results of a systematic review of reasons in favor and against genome editing in non-human animals that have been reported in the academic literature. This analysis leads to the identification of various important ethical themes and challenges as well as the formulation of several key recommendations for the academic debate on genome editing and GDTs.

As was set out in the previous section, empirical ethics research can help to identify important ethical questions, implications and challenges, and to elucidate how important stakeholders view and weigh different ethical aspects (80). In chapter 3 and 4, the results of an interview study amongst GDT experts from a variety of disciplines are discussed. **Chapter 3** focuses on the substantive ethical questions, concerns, and implications of GDTs, i.e. those questions, concerns, and implications that relate to "what is right in terms of duties, rights, and values (..) independent of any decision-making procedure" (p. 155) (86). The obtained insights provide stepping-stones for a constructive debate on the ethical implications and challenges of GDTs and call attention to topics that deserve further normative reflection. **Chapter 4** focuses on the procedural ethical questions and implications of GDTs, i.e. the questions, concerns and implications that relate to the process of decision-making about and governance of GDTs. This gives rise to recommendations for the development and evaluation of GDT governance. Moreover, this analysis points to unresolved normative questions that need to be addressed to move from general moral principles to concrete obligations that can guide GDT governance.

In **Chapter 5**, the ethical challenges that are brought about by GDTs are represented in a way that sparks the imagination and that reaches a broader range of publics than academic articles: through photographs. Whereas philosophical questions are often raised and analyzed in written texts, pictures may be a more accessible and intuitive way to incite reflection on the impact that emerging technologies may have on our lives and the world around us. In this way, these photographs contribute to facilitating public awareness and debate on GDTs.

Part II: Ethical landscaping – evaluating responsible development and governance of GDTs

The second part of this thesis explores what may be called 'ethical landscaping' by evaluating how the ethical landscape *should* be designed or influenced, i.e. whether and how GDTs can be developed and governed in an ethically responsible manner. In doing so, three specific ethical questions and concerns with regards to GDT development and governance are evaluated in more detail.

A first important set of ethical questions and concerns with regards to GDTs relates to the moral permissibility of intervening in nature in this way to target vector-borne diseases such as malaria. **Chapter 6** engages with some of these concerns by evaluating whether the inherent worth of mosquitoes may provide reason to refrain from using GDTs. It is argued that even if one adopts the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes equal inherent worth to all life forms – it can be considered morally permissible to modify or eradicate malaria mosquitoes using GDTs if specific conditions are met.

A second issue that is evaluated is the use of 'ethical licensing' in the context of GDTs and other biotechnologies. Patents are 'rights of exclusivity' that can be used to achieve private governance by controlling who is allowed to get a license and under what conditions. In **Chapter 7**, it is argued that the use of exclusivity rights for private governance raises procedural justice concerns and discussed why procedural justice matters. Subsequently, a potential solution to mitigate these concerns is proposed.

A third matter that is analyzed concerns the definition and delineation of 'community' in field trials with gene drive organisms. An important point of discussion regarding these field trials relates to who should be informed, consulted, and involved in decision-making about their design and launch. It is generally argued that community members in particular have a strong claim to be involved in such decision-making. Nonetheless, disagreement and unclarity exists about how this 'community' should be defined and delineated. This 'boundary problem' is evaluated in **Chapter 8**, in which it is explicated why it is important to define and delineate the community, and argued that geographical, affected, cultural, and political communities should be distinguished in discussions on community engagement in GDT research. Finally, initial guidance is proposed to decide how the community should be defined and delineated in this context.

Part III: General Discussion

The third part of this thesis deepens and broadens these analyses by answering this thesis' sub-questions. **Chapter 9** discusses its main results and conclusions and places this thesis' main findings in a broader perspective to determine what lessons can be learnt for ethics parallel research as an approach for early ethical guidance of new and emerging technologies more generally. Moreover, key recommendations for GDT development and questions for future research are proposed and identified.

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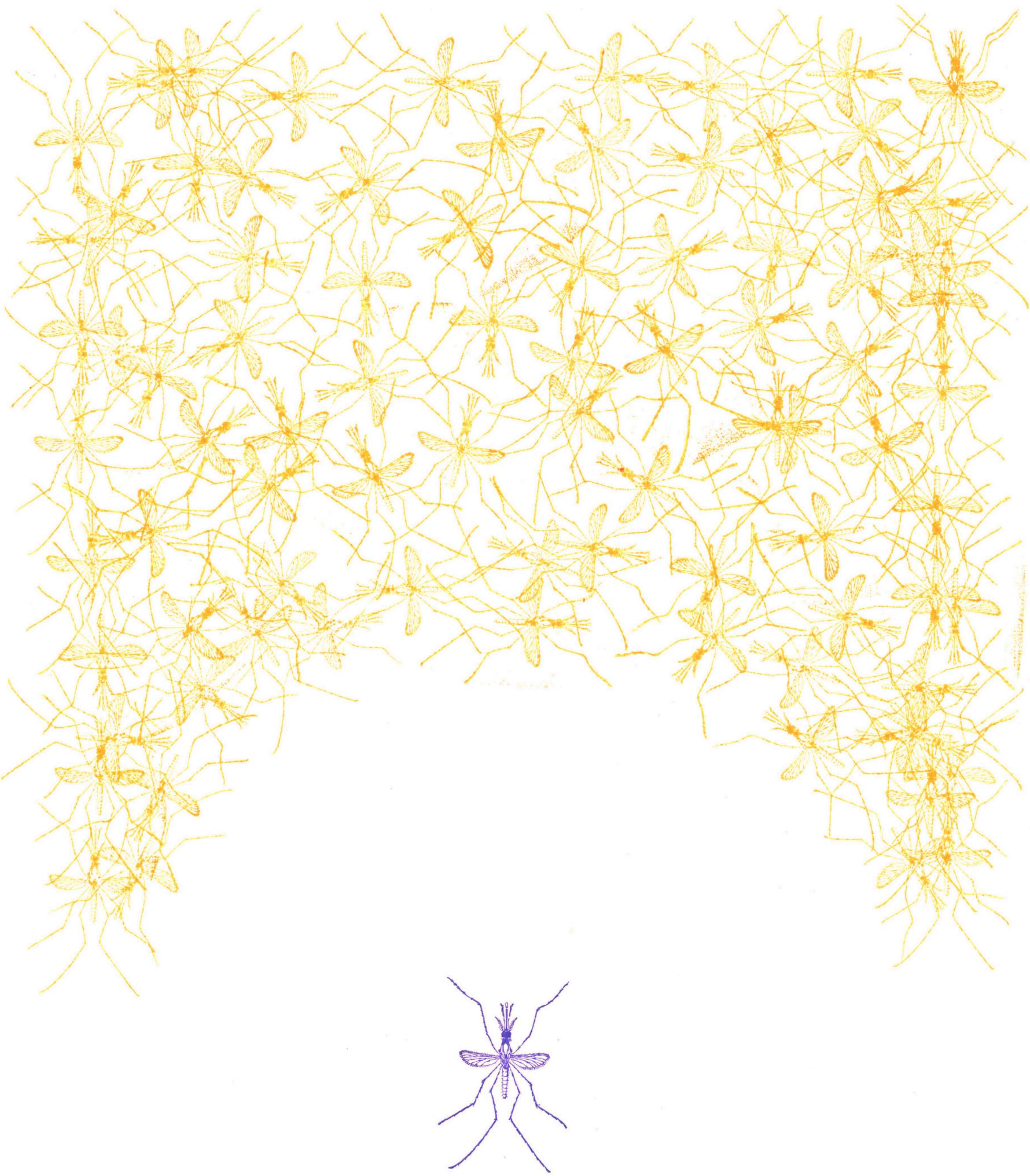
I

THE ETHICAL LANDSCAPE – IDENTIFYING THE ETHICAL CHALLENGES OF GENE DRIVE TECHNOLOGIES



2

THE ETHICS OF GENOME EDITING IN NON-HUMAN ANIMALS: A SYSTEMATIC REVIEW OF REASONS REPORTED IN THE ACADEMIC LITERATURE

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Abstract

In recent years, new genome editing technologies have emerged that can edit the genome of non-human animals with progressively increasing efficiency. Despite ongoing academic debate about the ethical implications of these technologies, no comprehensive overview of this debate exists. To address this gap in the literature, we conducted a systematic review of the reasons reported in the academic literature for and against the development and use of genome editing technologies in animals. Most included articles were written by academics from the biomedical or animal sciences. The reported reasons related to seven themes: human health, efficiency, risks and uncertainty, public acceptability, animal welfare, animal dignity, and environmental considerations. Our findings illuminate several important considerations about the academic debate, including a low disciplinary diversity in the contributing academics, a scarcity of systematic comparisons of potential consequences of using these technologies, an underrepresentation of animal interests, and a disjunction between the public and academic debate on this topic. As such, this article can be considered a call for a broad range of academics to get increasingly involved in the discussion about genome editing, to incorporate animal interests and systematic comparisons, and to further discuss the aims and methods of public involvement.

Introduction

In the last two decades, a host of genome editing technologies has emerged that can edit the genome with progressively increasing efficiency and ease of use. These technologies are based on the use of sequence-specific engineered nucleases, such as Zinc Finger Nucleases (ZFN) (1), meganucleases (2), and Transcription Activator-Like Effector Nucleases (TALEN) (3). In more recent years, genome editing was revolutionized by the emergence of Clustered Regularly Interspaced Palindromic Repeats (CRISPR) and the CRISPR associated protein 9 (Cas9) (4). In parallel, new applications of these genome editing technologies have emerged, such as CRISPR-based gene drive technologies (GDTs), which allow the rapid and super-Mendelian spread of a genetic element within a population or even a species (5,6).

Overall, this new generation of genome editing technologies allows scientists to modify the genomes of non-human animals (from here on: 'animals') more precisely than classical transgenesis (7) with comparably fewer off-target effects (8). Furthermore, engineered nucleases can introduce genetic changes without the use of foreign DNA (9). These genome editing technologies have a broad range of possible applications in animals, including to increase livestock productivity and disease resistance (10), create new animal models to study human disease (11), protect native species by eradicating invasive species, decrease or even eliminate vector-borne diseases such as malaria, and perhaps even resurrect extinct species (5,12). Understandably, these technologies and their applications have sparked both excitement and apprehension, raising new questions on ethics and governance and generating significant debate in both academic and public spaces.

Despite this ongoing debate, to our knowledge no comprehensive overview of the arguments raised in the academic discourse on genome editing in animals exists. Such an overview is a valuable contribution to the academic literature, as it provides insights into patterns of argumentation in the expert debate and can help uncover arguments that go unmentioned or are insufficiently conceptualized. It is particularly salient to study the academic debate since academic experts influence related science and technology policy and governance decisions (13–15). Moreover, insight into the academic debate is important for understanding whether it differs from the public debate and arguments. For technologies that have high societal impact, such as genome editing, it is important to identify and bridge potential gaps between the public and academic discourse in the early phases of development.

In this article, we present such a comprehensive overview by reporting the reasons for and against the development and use of genome editing technologies in animals as these have been mentioned in the academic literature. We then critically assess the academic debate and identify perspectives, issues and arguments that are underrepresented in the existing literature.

Methods

A systematic review of the reasons that have been given for and against the development and use of new-generation genome editing technologies in animals was conducted. This review was based on the method developed by Strech & Sofaer (16), which can be used to systematically identify reasons and arguments in favor of or against particular (normative or descriptive) positions or claims. This method does not assess the adequacy, quality or normative weight of the reported reasons (16), but enables a systematic collection of all the relevant literature in which an opinion, point of view, or position is put forward. Subsequently, it allows for an equally systematic extraction and synthesis of the reasons. It incorporates relevant items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (17) as well as thematic analysis typical of qualitative research (16).

Search strategy

A literature search of the PubMed, Web of Science, Scopus, CAB Abstracts and Philosopher's Index databases was conducted to find relevant articles. The choice for databases was discussed with experienced librarians; these five databases were selected as they cover a comprehensive area of biomedical, veterinary, and ethics research journals and articles. A search strategy that combined search terms for genome editing, animals (adapted from Hooijmans, Tillema, Leenaars & Ritskes-Hoitinga (18)), and ethics was used (see Appendix 1).

Article selection and inclusion criteria

Academic articles or book chapters written in English or Dutch, published in 2010 or later, were eligible for inclusion. Publications that did not contain a reason for or against the development or use of new-generation genome editing technologies in animals were excluded. Publications that specifically focused on older techniques (e.g. classical transgenesis) were also excluded.

Two researchers independently screened the titles and abstracts and, if applicable, the full texts of the articles. In case of disagreement about inclusion or exclusion, differences were discussed until consensus was reached. The reference lists of included articles were subsequently screened for additional relevant articles.

Data extraction and analysis

The full text of the selected articles was analyzed using a data extraction document (Appendix 2) that was designed prior to starting the data extraction to extract data in a systematic way. The contextual data of the included articles, including the discipline of the author(s) and the specific technologies and applications discussed, were also included. Subsequently, all the reasons for and against the development and use of new-generation genome editing technologies in animals were extracted. The reasons that were mentioned in the included articles ('reason mentions') were subsequently compared. If different articles mentioned the same reason, these were bundled under the same 'narrow reason'. Next, a list of narrow reasons was generated: for each narrow reason, we noted which article included that reason and the number of times it was mentioned.

Additionally, the narrow reasons were used to generate an overview of broader themes to which the narrow reasons related. If a narrow reason applied to two themes, the narrow reason was listed under the most applicable theme, as determined by consensus amongst the researchers. The formulation of both the narrow reasons and themes was an iterative process in which the categories were re-evaluated amongst all researchers several times to bundle similar narrow reasons together, categorize them and define the themes that best encompassed the narrow reasons.

Finally, an overview of the themes and narrow reasons was created by listing these in a table under the overarching classifications of 'human-related', 'animal-related', or 'environment-related' reasons in order of frequency of appearance. Within each theme, the narrow reasons mentioned in the literature were subcategorized as reasons for or against genome editing in animals; these subcategories were similarly listed in order of frequency of appearance. Where applicable, rebuttals of reasons in favor of genome editing were listed in the subcategory 'against' and vice versa.

Results

The database searches resulted in a total of 760 unique records. After title/abstract screening, full-text screening, and cross-referencing, 134 articles were included for data extraction and analysis (Figure 1).

Author affiliation

The included articles were written by professionals working primarily in academic institutions, in a variety of different departments or divisions: biomedical or biological sciences (n = 77/134), animal sciences (n = 30/134), ethics (n = 20/134), philosophy (n = 14/134), biotechnology companies (n = 8/134), governmental organizations (n = 6/134), law (n = 5/134), (bio)engineering (n = 4/134), nutritional or food sciences (n = 3/134), agricultural sciences (n = 3/134), consultancy (n = 2/134), epidemiology (n = 2/134), political sciences (n = 2/134), bioinformatics or computational biology (n = 2/134), psychology (n = 1/134), mathematics (n = 1/134), public and international affairs (n = 1/134) and a private foundation (n = 1/134). In 10/134 articles no author affiliation was listed (Table 1).

Figure 1: Flow chart of article selection and inclusion

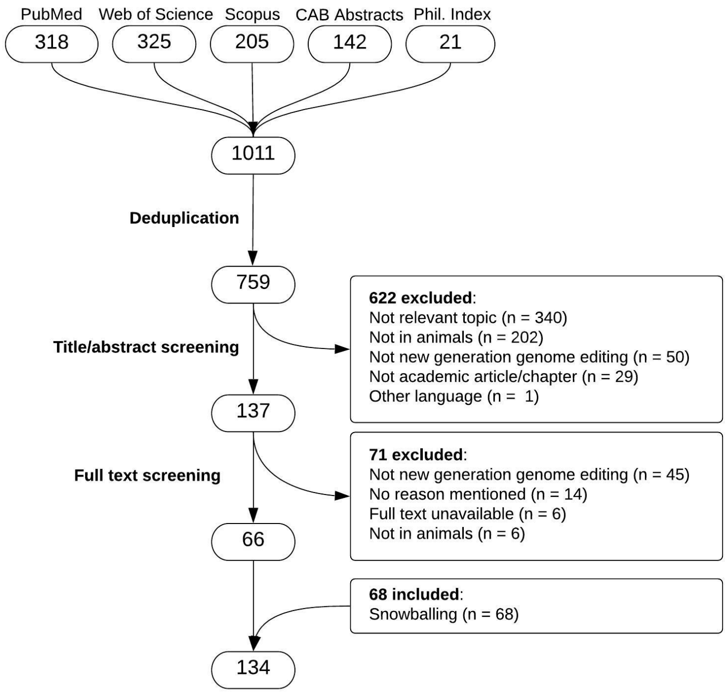

Table 1. Flow chart of article selection and inclusion

Author affiliation or discipline	*N**	*References*
Biological or (bio)medical sciences	77	(3–6,19,21,23,27,29,34–40,42,46,47,49,53–55,57,58,60,62,64–67,69–71,75,76,78–80, 82–92,95–108,111,112,117,120,121,124, 128–131,140,142)
Veterinary medicine or animal sciences	30	(10,11,19,21,34,57,59,68–70,72,74,75,80,82,90,92,97,101,103, 108,113,114,116,124,125,128–130,133)
Ethics	20	(6,20,22,23,28–31,43,48,51,52,78,81,91,93,107, 111,135,141)
Philosophy	14	(9,26,40,78,112,115,123,132,134,136–139,143)
No affiliation or no author listed	10	(7,32,41,44,50,56,63,94,118,126)
Biotechnology company	8	(10,21,73,92,103,104,108,119)
Governmental organization	6	(19,24,39,120,130,133)
Law	5	(12,23,122,127,139)
(Bio)engineering	4	(71,75,77,92)
Nutritional or food sciences	3	(25,33,109)
Agricultural sciences	3	(73,110,133)
Consultancy	2	(79,115)
Epidemiology	2	(19,93)
Political sciences	2	(25,39)
Bioinformatics or computational biology	2	(39,71)
Psychology	1	(27)
Mathematics	1	(38)
Public and international affairs	1	(45)
Private foundation	1	(6)

* Numbers add up to more than 134 as various included articles were written by authors with different affiliations or multiple affiliations.

Reasons for and against new-generation genome editing in animals

In total, 115 different reasons were mentioned in the reviewed articles; 67 of these reasons were in favor of and 48 against the development and use of new-generation genome editing in animals. The included articles contained from 1 up to 13 different reasons. The reasons were in response to a broad range of potential applications of genome editing in animals (Table 2).

These narrow reasons were subsequently categorized into seven broad themes: (1) human health; (2) efficiency; (3) risks and uncertainty; (4) public acceptability; (5) animal welfare; (6) animal dignity and species-specific capacities; (7) environmental considerations (Table 3). In the following sections, the different broad and narrow reasons are discussed in more detail.

Table 2. Potential applications of genome editing in animals mentioned in the literature

Potential application of genome editing in animals	*(Potential) aim*
Genome editing in general	
Create an animal model of Parkinson's disease (11)	Create animal models of human disease
Delete an antigen that causes hyperacute rejection in pig-to-human transplantation (76) or inactivate porcine endogenous retroviruses (PERV) to prevent transmission of these viruses to humans (103)	Facilitate xenotransplantation from pigs to humans by reducing the chance of immune rejection
Increase skeletal muscle mass and thereby meat production (70)	Increase nutritional value for humans; increase production efficiency in animal farming
Create a chicken strain with low allergenicity (41)	Decrease allergic reactions in humans
Increase disease resistance to Porcine Reproductive and Respiratory Syndrome in livestock (116)	Decrease suffering of farm animals; increase production efficiency; reduce use of antibiotics
Create polled (hornless) cattle (108)	Decrease suffering of farm animals (by preventing painful dehorning); decrease costs; increase production efficiency; decrease moral distress of farmers
Produce poultry in which the embryo's sex can be recognized in the egg, in which genetic males become phenotypical females, or in which male embryos die during early development (133)	Decrease suffering of farm animals by preventing the killing of male chicks
Create so-called 'diminished' animals in which the ability to sense pain is impaired (107)	Decreasing suffering of animals in research and farming
Revive the woolly mammoth as a major grazing animal in the Arctic (112,142)	Curiosity; advance scientific understanding; restore an Arctic steppe in the place of the less ecologically rich tundra (25)
GDTs	
Induce mosquito resistance to malaria parasites (36); induce infertility in mosquitos (48)	Reduce the burden of vector-borne diseases
Reduce fertility or bias sex towards males in invasive species, creating a population that is not reproductively viable (120)	Control or eradicate invasive species
Increase genetic gain in breeding programs (10)	Increase economic productivity in animal farming
Change reproductive behavior of wild animals that give birth to large numbers of offspring, many of whom do not survive to adulthood, by decreasing the number of offspring they produce per cycle (26)	Prevent wild animal suffering

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Table 3. Reasons for and against the development and/or use of genome editing technologies in animals

		n	References	Technologies
Human-related reasons				
Human health				
For (n=8)	Could improve human health by reducing the burden of vector-borne diseases such as malaria	36	(5,6,19–52)	GDTs; genetic modification (GM); genome editing
	Could enhance research by creating better animal model systems of human disease	35	(3,4,7,11,25,27, 29,31,33,53–78)	Various (ZFN, TALEN, CRISPR); genome editing
	Could facilitate xenotransplantation, which could be a solution to the human donor shortage	26	(22,24,25,27,31,33, 55,58,65,66,68–70, 72,73,75,76,82,83, 89,91–106)	Various (ZFN, TALEN, CRISPR)
	Could expedite research in other species, including non-human primates, which provide more accurate models for human (neurological) disease	12	(41,54,64, 82–90)	CRISPR
	Could help to meet the challenge of producing more food more sustainably to ensure the future global population can be fed	6	(45,78,107–110)	Various (ZFN, TALEN); GM
	Could improve human health through the provision of new medicines and therapies	4	(27,33,41,73)	Various (TALEN, CRISPR)
	Could enable genome engineering in non-human primates; this could be considered ethically problematic, but it is much more ethically problematic to watch people die who could be saved	1	(86)	CRISPR
	Could be used to create a chicken strain with low allergenicity	1	(41)	CRISPR
Against (n=8)	Re simplifying and speeding up the production of new transgenic animal models of human disease: most of such models fail to directly benefit humans; this lack of reproducibility may put human research participants at risk at a later stage	3	(79–81)	CRISPR
	Re bringing routine genome engineering of non-human primates within reach, which could help identify genetic underpinnings of disease or develop therapies: the moral permissibility of this approach is questionable given available alternatives	2	(41,81)	CRISPR
	Could pose risks to human health if genetic modification is not successful in creating mosquitoes resistant to infections, but instead confers no resistance or actually reduces resistance to the target infection	2	(43,51)	GM; GDTs
	Could disrupt ecosystems, which could be harmful to human populations depending on them	2	(40,45)	GDTs
	Could be used to re-create species that may become a vector or reservoir for viruses that can be harmful for human beings	1	(112)	Genetic engineering
	Re use to create a chicken strain with low allergenicity: there may not be a compelling need for doing so since allergy usually only occurs in children, and alternatives and egg substitutes are available	1	(111)	Various (ZFN, TALEN, CRISPR)
	Re use to produce better quality food: little is known about the effects these modified organisms would have on humans when consumed	1	(53)	CRISPR
	Could increase productivity of the livestock sector: this is an undesirable outcome given the negative impact of meat consumption on human health	1	(20)	Various (ZFN, TALEN, CRISPR)

2

Table 3. Continued

		n	References	Technologies
Efficiency				
For (n=14)	Could be more efficient, versatile, precise, easy to use or accurate than previous editing technologies	39	(3,4,6,7,9,22,26, 33,41,42,53,55, 60–64,67,71,73, 75,76,78,79,81, 83,85,91,99, 105,108,110, 116–122)	Various (ZFN, TALEN, CRISPR)
	Could lead to advances in scientific understanding or technological advances	9	(12,27,42,47, 51,99,105, 112,119)	Various (ZFN, TALEN, CRISPR; GM; active genetics*)
	Could be relatively inexpensive in comparison to previous approaches	9	(9,19,26,27,40, 78,81,110,126)	CRISPR, GDTs
	Could save costs for the farming industry	9	(29,41,100,105, 108,113,116, 128,129)	Various (ZFNs, TALEN, CRISPR)
	Could accelerate and/or enhance the trait improvement currently accomplished by classic breeding	8	(10,33,69,72, 108, 110,124, 125)	Various (ZFN, TALEN, CRISPR, GDTs)
	Could increase production efficiency	7	(25,29,70,73, 100, 113,115)	Various (ZFNs, TALEN, CRISPR); GM
	Could be a potentially efficient and rapid tool to improve important traits in livestock	3	(27,113,114)	Various (ZFNs, TALEN, CRISPR)
	Could be a cost-effective strategy to control the transmission of vector-borne diseases	3	(6,34,51)	GM, GDTs
	Could increase economic productivity in animals bred for human consumption	2	(114,127)	Various (ZFNs, TALEN, CRISPR); genetic engineering
	Could provide animals with disease resistance, which could reduce the overuse of antibiotics	2	(25,116)	Various (TALEN, CRISPR)
	Could be used to eradicate vector-borne diseases in a more efficacious and/or logistically less complex way than other efforts to eliminate these diseases	2	(34,35)	GDTs
	Could be used for pest control, being more precise or effective than other pest management methods such as pesticides	2	(40,43)	GDTs
	Re the possibility of off-target effects: these are fewer and more controlled compared with the mutations that are caused by generally accepted technologies such as conventional breeding	2	(110,111)	Various (ZFNs, TALEN, CRISPR)
	Re the possibility of off-target effects: these can be minimized by careful design and testing, and their effects are largely identical to those of the natural processes that continually create variation in the genomes of food animals	1	(124)	Various (ZFNs, TALEN, CRISPR
Against (n=1)	Could still have inadequate gene targeting efficiency, off-target effects, or cause mosaic mutations	10	(62,69,74,80, 83,84, 87–89, 106,123)	Various (ZFN, TALEN, CRISPR)
Risks & uncertainty				
Against (n=8)	Could spread beyond its target population due to accidental release, cross-breeding, or gene flow; this release could have unpredictable ecological consequences	12	(19,28,35,40, 43,45, 50,53, 117,120,130,131)	GDTs
	Could introduce off-target mutations into the gene pool and spread these across a species	5	(7,40,45,53,120)	GDTs
	Could have novel features that are unprecedented and unexpected, so the risks and consequences are difficult or even impossible to characterize beforehand	4	(40,45,51,132)	Various (synthetic biology, GDTs, GM)

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Table 3. Continued

		n	References	Technologies
	Could involve risks of deliberate release of (disease carrying (19)) genetically modified mosquitoes to the environment	2	(22,132)	Synthetic biology (incl. genome editing), GDTs
	Could be used to serve the (economic) interests of particular groups with little concern for the general interest	2	(40,115)	Various (ZFNs, TALEN, CRISPR, GDTs)
	Could have unexpected effects since our knowledge & understanding of the genetic background of complex traits is incomplete	1	(113)	Various (ZFNs, TALEN, CRISPR)
	Could have non-negligible risks because breaches of containment are impossible to rule out and, once released, just a few escaped genetically modified mosquitoes could be capable of spreading transgenes on a global scale	1	(49)	GDTs
	Could benefit humans if used for applications to human disease and agricultural production, however these applications could primarily benefit the current generation, with secondary benefits and potential risks placed upon future generations	1	(45)	GDTs
For (n=7)	Re the potential to spread beyond its target population or have unintended consequences: various GDT designs and other containment measures may mitigate these risks	13	(5,19,22,23,27, 29,32,38,39, 51,118,130, 131)	GDTs
	Re novel features: could be considered similar to conventional breeding due to the similarity to natural mutations and absence of transgenes	4	(69,70,111,124)	Various (ZFNs, TALEN, CRISPR)
	Re potential risks: could be researched in a phased approach, allowing sufficient time to evaluate the efficacy and safety of GDTs before regulatory decisions are made on whether they will be suitable for use	2	(24,39)	GDTs
	Re potential for off-target effects with negative effects: genome modification is more precise and consequently has far fewer risks than conventional breeding	1	(108)	Various (ZFN, TALEN)
	Re potential risks: it is generally more difficult to prove that something is safe than to find potential risks; the damage of not using a new technique may exceed its potential risks	1	(113)	Various (ZFNs, TALEN, CRISPR)
	Re uncertain consequences: these are not in itself a sufficient reason not to use the technology; the magnitude and likelihood of these risks ought to be thoroughly analyzed and balanced against the potential benefits	1	(48)	GDTs
	Re potential risks: these ought to be balanced with the risks and harm caused by the unmodified wild-type	1	(19)	GDTs
Public acceptability				
For (n=6)	Could be more acceptable to the public than previous technologies, as no foreign DNA is introduced	4	(9,42,113,114)	Various (ZFNs, TALEN, CRISPR)
	Could increase the chance of a publicly justified policy permitting genome editing	1	(9)	CRISPR
	Could be less controversial than using pesticides for pest control	1	(40)	GDTs
	Could impact community members who have not consented to the release of genetically modified mosquitoes, however this may be justifiable if the public health benefits of the trial for the community are important enough	1	(51)	GM
	Could be used in field trials with genetically modified animals whilst respecting the interests of community members if community advisory boards and a community authorization process are used	1	(30)	GDTs
	Re public resistance: could lead to resistance when modified mosquitoes cross borders to communities who did not agree with this, however various designs of the GDTs may prevent this, enabling local communities to make local decisions	1	(38)	GDTs
Against (n=1)	Could lead to public resistance	6	(12,31,41,49, 51,131)	GDTs; GM; genome editing, genetic engineering

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Table 3. Continued

		n	References	Technologies
Animal-related reasons				
Animal welfare				
For (n=13)	Could decrease animal suffering in dairy farming by creating dehorned cattle, preventing invasive and painful dehorning	10	(9,25,29,33,41, 107, 108,111, 113,124)	Various (ZFNs, TALEN, CRISPR)
	Could counter welfare problems by creating so-called 'diminished animals' in which the ability to sense pain is impaired	8	(107,115,123, 127,135–138)	Genome editing (CRISPR); genetic engineering; GM
	Could increase animal health and welfare by providing animals with disease resistance	8	(24,25,41,73, 107,111,113,116)	Various (ZFNs, TALEN, CRISPR)
	Could increase adaptations to different environmental conditions	2	(29,127)	Various (ZFNs, TALEN, CRISPR); genetic engineering
	Could be used to prevent the killing of day-old male chicks	2	(41,133)	CRISPR; GM
	Re the possible creation of animals with welfare problems: if they have a life worth living we cannot say that they are worse off due to the genetic modification, for if they had not been created with genetic modification, they would not have existed at all	2	(115,134)	GM
	Re off-target effects: could result in fewer off-target effects than previous techniques, which could improve welfare of genetically modified animals	1	(9)	CRISPR
	Could be used to decrease the suffering of research animals	1	(79,81)	CRISPR
	Could remove known harmful recessive alleles that impair fertility or health and in that sense repair accumulated damage in the genome of breeding animals	1	(113)	Various (ZFNs, TALEN, CRISPR)
	Could prevent wild animal suffering by using genome editing to change reproductive behavior; the harm that would be prevented by doing so would outweigh the harm of developing and testing these strategies	1	(26)	CRISPR
	Could lead us to ignore the predicament of the animal and to accept negative effects on animal welfare for the sake of other goals, however this concern may be addressed by using less drastic GDT designs and using these promote animal welfare	1	(9)	GDTs
	Re applications that would permit even greater intensification of farming resulting in decreased animal welfare: this seems unlikely given recent trends of companies to improve animal welfare	1	(107)	Various (ZFNs, TALEN, CRISPR)
	Could be a humane method to eliminate invasive species	1	(6)	GDTs
Against (n=11)	Could result in off-target mutations or unintended effects, which could negatively affect animal health	6	(9,20,25,45,111, 140)	Various (ZFNs, TALEN, CRISPR)
	Could contribute to animal suffering by perpetuating the use of animals in research	5	(9,31,54,79,81)	Genome editing; CRISPR
	Could result in secondary complications that are bad for animal welfare (e.g. increased muscle growth could lead to increased rates of Caesarean sections, leg problems, or breathing complications)	3	(20,111,113)	Various (ZFNs, TALEN, CRISPR)
	Could be used for applications that would permit even greater intensification of farming; this outcome would be undesirable	3	(20,54,123)	Various (ZFNs, TALEN, CRISPR); genome engineering
	Could be used to decrease animal suffering (by creating polled cattle or diminished animals), however there are alternatives to doing so (e.g. by improving animals' environments)	2	(111,134)	Various (ZFNs, TALEN, CRISPR)
	Could be combined with somatic cell nuclear transfer cloning to deliver the nuclease-mediated genetic alterations, which is associated with embryonic losses, postnatal death, and birth defects	2	(74,114)	Various (ZFNs, TALEN, CRISPR)
	Could bring routine genome editing of non-human primates within reach; this use of the technologies may substantially diminish these organisms' welfare and quality of life	1	(81)	CRISPR

Table 3. Continued

		n	References	Technologies
	Re use to preventing wild animal suffering: the complexity of ecosystems, the unpredictability of climate change and the indeterminacy of human behavior leaves us with too little confidence that this aim will be successful	1	(139)	Genome editing
	Re use to create diminished animals who lack the affective dimension of pain: no proof-of-concept experiment has been done on farm animals and conducting these experiments would itself cause suffering	1	(123)	Genetic engineering
	Re use to reviving extinct species: the revived animals may end up suffering either as a result of the processes used or because of their particular genomic variations	1	(12)	Genetic engineering
	Re use to re-create species: these may become a vector or reservoir for viruses that can be harmful for other animals	1	(112)	Genetic engineering
Animal dignity & species-specific characteristics				
Against (n=9)	Could be objectionable since it instrumentalizes animals by using them as mere objects to serve human purposes	5	(20,54,91, 112,115)	Various (ZFNs, TALEN, CRISPR);
	Could be used to revive extinct species or create gene-edited pets, but it is questionable if physiological limits should be altered or animals should be exploited for unimportant human purposes like entertainment	3	(12,41,56)	Various (TALEN, CRISPR)
	Could impinge on animal's dignity as altering the genome of an animal is a failure to acknowledge its dignity or prevent the animal from living according to its instinct	3	(54,93,113)	Various (ZFNs, TALEN, CRISPR)
	Could affect the 'telos' (the essence and purpose of a creature) if they are genetically altered to the point where they lose the behavior that characterizes that animal	3	(111,127,137)	Various (ZFNs, TALEN, CRISPR); GM
	Could expedite transgenesis in other species, including non-human primates, which likely occupy a level of moral status that would obligate us to protect them from being used in this way or to allow it only in extremely exceptional circumstances	2	(79,81)	CRISPR
	Could create diminished animals to decrease animal suffering, but this is an inappropriate response to the historical wronging of agricultural animals; we have a duty to repair these wrongs	2	(123,136)	Genome editing (CRISPR)
	Could only be rightfully done if the permissibility of genome editing in research is evaluated for each species on its own merits	1	(54)	CRISPR
	Could be used to facilitate xenotransplantation, which could be considered ethically untenable as it compromises species boundaries	1	(91)	CRISPR
	Could be viewed as the initiation of increasingly imbalanced power distribution between humans and animals	1	(111)	Various (ZFNs, TALEN, CRISPR)
For (n=11)	Re breaching species norms if used for animal diminishment: species norms are only indirectly morally significant, as a generally useful guide to evaluating animal welfare	2	(134,136)	Genome editing (CRISPR)
	Re violating animal dignity or integrity: such arguments focus only on respect for individual animals, they ultimately cannot justify an objection that is based on a species-norm, as is the case in the discussion on enhancement	2	(115,134)	GM
	Re use to create diminished animals, which could be said to harm these animals as their species-typical essence would be changed: as the literature about human disability has taught us, we should not assume that 'disabilities' caused by diminishment make animals worse off	2	(107,135)	Various (ZFNs, TALEN, CRISPR; genetic engineering
	Re violating rights, violating dignity or wrongly instrumentalizing: genome editing determines which individual will come into existence rather than modifying existing individuals, making it hard to say how its rights could have been infringed, its dignity violated, or even that it has been wrongly instrumentalized	1	(136)	Genome editing (CRISPR)
	Re breaching the sanctity of the lives of mosquitoes by making them go extinct: neither existing mosquitoes nor the species holistically bear a significant degree of moral status	1	(48)	GDTs

Table 3. Continued

		n	References	Technologies
	Re impinging on an animal's dignity by making them serve better as objects for human use: the Kantian concept of dignity cannot be applied to animals, for this concept is tied to prerequisite conditions that animals do not possess	1	(141)	Genetic engineering
	Re use to modify an animal's telos or nature: this could be morally acceptable if the animals are made less miserable or happier as one does not morally wrong the telos by changing it; only individuals can be wronged	1	(138)	Genetic engineering
	Could be used to prevent additional violations to animal rights, which would be preferable to the status quo, even on an account that considers raising animals for human consumption impermissible	1	(107)	Various (ZFNs, TALEN, CRISPR
	Re impinging on an animal's integrity or dignity and thereby harming him even if welfare is improved: what is good for an individual must in some way resonate with that individual; what is good for him cannot diverge from his welfare	1	(107)	Various (ZFNs, TALEN, CRISPR)
	Re impact on the 'telos' of an animal: the animal's telos can still be respected if it is provided with an environment that fits its altered genetic predispositions	1	(107)	Various (ZFNs, TALEN, CRISPR)
	Re impact on the 'telos' of an animal: the idea that there is some 'true essence' of a species is mistaken as behaviors and tendencies change over time, making it hard to see why this should be seen as morally problematic	1	(107)	Various (ZFNs, TALEN, CRISPR)
Environment-related reasons				
Environmental considerations				
Against (n=10)	Could have unknown negative effects on ecosystems	13	(6,7,25,28,31,35, 40,41,45,53,78, 117,120)	GDTs
	Could cross moral limits by exceeding the extent to which humans breach natural boundaries or act out of hubris; nature/life cannot be completely manufactured or planned and we ought to acknowledge their unpredictability	4	(12,54,115,132)	Various (ZFNs, TALEN, CRISPR, synthetic biology)
	Could constitute an unnatural interference with nature	2	(115,133)	Various (ZFNs, TALEN, CRISPR); GM
	Could be used to revive extinct species, for which there may no longer be a niche	2	(12,112)	Genetic engineering
	Could be used to revive extinct species, which might diminish the desire to protect existing species	2	(12,112)	Genetic engineering
	Re use to revive extinct species: genome editing will fail to genuinely recreate species while preserving their species identity	2	(12,143)	Genome editing; genetic engineering
	Could disrupt the natural order; although this order should not hold an intrinsic moral value, deleting genetic diversity could carry risks by deleting traits that are advantageous	1	(22)	GDTs
	Could lead to increased productivity of the livestock section, which is not desirable given the negative impact of this sector on the environment (e.g. greenhouse gas production & water and land pollution)	1	(20)	Various (ZFNs, TALEN, CRISPR)
	Could be used to control certain invasive species; if this succeeds, this could become a Trojan horse to legitimate the eradication of other species without questioning to whom or what they are harmful	1	(40)	CRISPR, GDTs
	Could be more transformative, uncontrollable and ecologically damaging than organisms modified to contain self-limiting genes	1	(30)	GDTs
For (n=9)	Could enable ecological conservation by eradicating invasive species or reviving extinct species	8	(5,12,38,45, 47,50,52, 142)	Active genetics*; GDTs; genetic engineering
	Could help to develop and support more sustainable agricultural models	4	(5,22,38,39)	GDTs

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Table 3. Continued

	n	References	Technologies
Re potential to be considered unnatural or alike 'playing God': it is unclear what is meant by naturalness; furthermore, there is no reason to accept that the natural is necessarily good and the unnatural necessarily bad	2	(93,107)	Various (ZFNs, TALEN, CRISPR); genetic engineering
Could contribute to reducing the environmental impact of animal production	1	(113)	Various (ZFNs, TALEN, CRISPR)
Could protect threatened species and reduce invasive species to conserve the natural and cultural world for future generations, which could be imperative from an intergenerational justice perspective	1	(45)	GDTs
Re potential of driving mosquitoes to extinction being considered 'playing God' or displaying hubris: there may be sufficient reasons – such as saving many lives - that may justify improving the given	1	(48)	GDTs
Could be used to control agricultural pests; this may be a more environmentally sound control method than using insecticides	1	(19)	GDTs
Could be used to revive extinct species, which would be just; since humans killed extinct species and have the power to revive them, there is a duty to do so	1	(12)	Genetic engineering
Re ecological risks created by using GDTs to prevent wild animal suffering by using genome editing to change reproductive behavior: these risks may be offset by modifying other features of the ecosystem, too	1	(26)	CRISPR, GDTs

* Genetic manipulations in which a "genetic element is copied from one chromosome to the identical insertion site on the sister chromosome using Cas9 and guide RNA elements" (p. 55) (47)

(i) Human-related reasons

Human health

Most reasons in favor of genome editing in animals concerned its potential to improve human health. First, these hoped-for improvements included using genetic modification, genome editing or GDTs to reduce the burden of vector-borne diseases (5,6,19–52), either by suppressing or eradicating insect populations (47,48) or inducing vector resistance to disease pathogens (47,48). At the same time, however, some authors noted that GDTs could pose risks to human health if they disrupted ecosystems on which humans are dependent (40,45), or if modified mosquitoes did not confer resistance — or if they actually reduced instead of increased resistance to the target infection (43,51).

Second, various authors noted that genome editing in animals could enhance research in animal systems by creating better animal models of human disease (3,4,7,11,25,27,29,31,33,53–78) which could ultimately benefit human health, for example, by leading to the creation of new medicines and therapies (27,33,41,73). At the same time, it was argued that there is a lack of reproducibility of animal findings in humans (79–81), which could put human research participants at risk at a later stage of the research (81).

In a similar way, authors argued that genome editing could expedite research in other species, including non-human primates, which could provide more accurate models for human (neurological) disease (41,54,64,82–90). The permissibility of this approach was questioned, however, given available alternatives such as using organoids or stem cell models of disease (81) or using animal models of smaller animals such as mice (41). It was mentioned that although genome editing in non-human primates could be considered ethically problematic, it would be even more ethically problematic to let humans die who could be saved (86).

Third, genome editing in animals could provide a solution to the long-standing shortage of human organ donors by facilitating xenotransplantation from pigs into humans (24,25,27,33,58,68,69,73,75,76,91–106), either by reducing the chance of immune rejection in xenotransplantation (22,25,31,55,65,66,70,72,73,82,83,89,96,97,100–102) or by decreasing the risk of transmission of porcine pathogens such as porcine endogenous virus (PERV) (24,27,33,58,76,91,92,94,96,98,103,104,106). It was mentioned that this solution should be compared to alternative solutions to this problem in terms of resource allocation and prioritization (22).

Fourth, genome editing could help to meet the challenge of producing more food more sustainably to ensure that the future human population can be fed (45,78,107–110), for example, by increasing skeletal muscle mass and thereby meat production. Concurrently, it was mentioned that little is known about the effects these modified organisms would have on humans when consumed (53) and that it could be undesirable to increase meat production given the negative impact of meat consumption on human health (20).

Finally, the authors noted that genome editing could be used to create a chicken strain with low allergenicity, which could benefit humans with egg allergies (41). On the other hand, authors mentioned that there may not be a compelling need to produce such chickens because the allergy usually only occurs in children and because alternatives and egg substitutes are available (111). Finally, some authors noted that if genome editing were used to revive extinct species (also known as de-extinction), the re-created species could potentially be harmful to humans if it became a vector or reservoir for viruses (112).

Efficiency

Many reasons in favor of genome editing in animals mentioned the efficiency of these techniques. First, it was argued that genome editing could be a potentially efficient and rapid tool to improve important traits in livestock (27,113,114), which could increase production efficiency (25,29,70,73,100,113,115) for example, by achieving a higher meat yield (25,29,70,100,113). Various authors argued that genome editing using engineered nucleases (ZFN, TALEN or CRISPR) was more efficient, versatile, precise, easy to use or accurate than previous genetic technologies (3,4,6,7,9,22,26,33,41,42,53,55,60–64,67,71,73,75,76,78,79,81,83,85,91,99,105,108,110,116–122). On the other hand, it was argued that genome editing technologies could still have inadequate gene targeting efficiency and cause off-target effects or mosaic mutations (106), particularly in non-human primates (62,69,74,80,83,84,87–89,123). Other authors mentioned that these

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off-target effects could be identical to those of natural processes that continually create variation in the genomes of food animals (124), and that they could be fewer and more controlled than the mutations caused by generally accepted technologies such as conventional breeding (110,111). Finally, it was suggested that off-target effects could be minimized by careful design (124).

Second, authors compared the efficiency of these technologies to alternative strategies in which genome editing was not used. It was argued that genome editing could facilitate quicker or more effective trait improvement than classic breeding (10,33,69,72,108,110,124,125). For GDTs, it was mentioned that this technology could be more efficacious than other approaches at eliminating vector-borne diseases (34,35) or than other pest management methods such as pesticides (40,43).

Third, it was argued that these technologies could lead to advances in scientific understanding (12,27,42,47,51,99,105,112,119) or to technological advances (12). Authors also mentioned that genome editing could reduce the overuse of antibiotics in farm animals by providing these animals with disease resistance (25,116).

Fourth, issues of cost were addressed. It was mentioned that CRISPR could be relatively inexpensive in comparison to both previous genetic technologies (9,26,27,78,81,110,126), other pest management techniques such as insecticides (19,40) and traditional sterile insect methods (19), and that it could increase economic productivity in animals bred for human consumption (114,127). Moreover, authors mentioned that genome editing could save costs for the farming industry by providing animals with disease resistance (41,100,105,116,128) or by transferring polled genes to horned cattle, obviating the need for expensive dehorning (29,108,113,129). Finally, GDTs could be a cost-effective strategy for controlling the transmission of vector-borne diseases (6,34,51).

Risks and uncertainty

Other reasons given for or against the use of genome editing technologies concerned their potential risks and uncertainties.

For GDTs, the risks addressed primarily related to an accidental or deliberate release of gene drive organisms. It was mentioned that the genes drive could spread beyond their target population (45,53,120) owing to accidental release (19,28,35,40,50,117,130,131), horizontal transfer (35,43,45), cross-breeding (40) or gene flow (40), with unpredictable ecological consequences. Authors noted that it could be impossible to rule out breaches of containment, which would constitute a non-negligible risk as release of just a few gene drive organisms could cause the transgenes to spread on a global scale (49). Authors also mentioned that gene drive organisms could be released deliberately, exposing the public and the environment to risk (22,132), particularly if these organisms were engineered to carry diseases rather than prevent them (22). The potential for off-target mutations affecting the GDT was mentioned as another risk (7,40,45,53,120); guide RNA could, for example, mutate over time and consequently target an unintended part of the genome (7).

Several authors mentioned potential ways to mitigate these risks. Various GDT designs and other containment measures could mitigate unintended consequences or the risk that the change would spread beyond the target population (5,19,22,23,27,29,32,38,39,51,118,130,131). Authors also suggested that GDTs could be researched in a phased approach, allowing sufficient time to evaluate the efficacy and safety of gene drive organisms before regulatory decisions are made about whether they are suitable for widespread use (24,39). Furthermore, it was argued that these potential negative consequences are not in themselves a sufficient reason not to use GDTs; the magnitude and likelihood of these risks ought to be analyzed thoroughly and balanced against the potential benefits (48) as well as the risks and harm caused by the unmodified wild-type animal (19).

For genome editing in general, the uncertainty involved in assessing potential consequences of genome editing technologies was stressed. It was argued that the risks or consequences of genome editing technologies could be difficult or even impossible to characterize beforehand, given their novel features (40,45,51,132) and our incomplete knowledge and understanding of the genetic background of complex traits (113). With respect to applications of genome editing in animal farming, on the other hand, it was argued that genome editing could be considered similar to conventional breeding because the created modifications are comparable to natural mutations and no transgenes are involved (69,70,111,124). Although genome editing could result in off-target effects with potential negative consequences, it was argued that genome editing is more precise and therefore has fewer risks than conventional breeding and consequently should be generally regarded as safe (108). Some authors also argued that it is generally more difficult to prove that something is safe than to find potential risks; the damage of not using a new technique may exceed its potential risks (113).

Finally, it was mentioned that genome editing could be used to serve the (economic) interests of particular groups, such as the agriculture or food industry (40), with little concern for the public interest (40,115). Additionally, applications of GDTs to human disease and agricultural production could primarily benefit the current generation, with secondary benefits and potential risks placed upon future generations; it was argued that this may not be acceptable from a standpoint of intergenerational equity given the irreversibility and uncertainties inherent to the deployment of GDTs (45).

Public acceptability

Other human-related reasons in favor of or against genome editing in animals concerned public acceptance or rejection of the technologies. Some authors argued that the new generation of genome editing technologies might be more acceptable to the public than previous technologies because no foreign DNA is introduced into the animal (9,42,113,114). It was mentioned that this could consequently increase the chance of a publicly justified policy (9). It was also mentioned that the public might consider GDT applications in agriculture less controversial than using pesticides for pest control (40).

By contrast, it was argued that some uses of genome editing could generate public resistance to the technologies (12,31,41,49,51,131), for example, if public funds were used to bring back extinct species (12) or if genetically modified mosquitoes were to cross borders to other countries that did not support their release (49,51,131). Other authors asserted that the latter concern could be mitigated by using GDT designs that could enable local communities to make decisions concerning their own local environments (38). While authors acknowledged that it would not be possible to seek consent from all humans who could potentially be impacted by the release of genome-edited mosquitoes, it was argued that release could nonetheless be justified if the public health benefits of the trial are important enough for the community (51). It was suggested that one way to conduct field trials with genetically modified animals while respecting the interests of community members is to use community advisory boards and a community authority (30).

(ii) Animal-related reasons

Animal welfare

Reasons related to animal welfare were used to argue both in favor of and against genome editing in different types of animals.

First, it was argued that genome editing could decrease the suffering of farm animals. For example, genome editing could be used to prevent the killing of day-old male chicks (41,133) by enabling the production of poultry in which the embryo's sex can be recognized in the egg, in which genetic males become phenotypical females or in which male embryos die during early development. Authors also suggested that genome editing could be used to repair accumulated damage in the genome of breeding animals by removing harmful recessive alleles that impair animal fertility and health (113). Additionally, genome editing could be used to create hornless cattle, which would not require the painful dehorning that is commonly performed in the farming industry to protect both cows and farmers from injury (9,25,29,33,41,107,108, 111,113,124). At the same time, it was mentioned that this goal could be accomplished in other ways too; instead of creating polled animals, the rearing environment of cattle could be improved to prevent accidents, horn covers could be used, or dehorning could be performed under anesthesia (111,134).

Other authors emphasized the potential use of genome editing to increase animal health and welfare by making animals resistant to diseases (24,25,41,73,107,111,113,116) or better able to adapt to environmental conditions (29,127). By contrast, it was

argued that such uses of genome editing would enable even greater intensification of farming, for example, by generating polled or disease resistant animals that could be kept at higher density (20,54,123). While these authors noted that any intensification of farming would decrease animal welfare, others questioned the likelihood of this outcome given recent trends of companies improving animal welfare (107).

Some authors considered the possible use of genome editing to counter welfare problems of farm animals by creating the so-called diminished animals with an impaired ability to sense pain (107,115,123,127,135–138). In response, the authors noted that there is no proof-of-concept experiment for such an application in farm animals and argued that conducting these experiments would itself cause suffering (123). Lastly, authors noted that if farm animals were edited to improve production efficiency, some of these genome modifications could result in secondary complications that are bad for animal welfare (20,111,113); increased muscle growth, for example, could lead to increased rates of Caesarean sections, leg problems or breathing complications.

Second, it was argued that genome editing could be used to decrease the suffering of research animals, for example, by decreasing the occurrence of unwanted genetic effects (79) and reducing the number of animals used to create animal model systems compared to traditional methods (81). On the other hand, it was argued that, if genome editing were to be widely used, this decrease in suffering per experiment would be offset by the overall increase in the numbers of transgenic animals used in research (54,79); in this way, genome editing could contribute to animal suffering by perpetuating their continued use in research (9,31,54,79). Moreover, it was mentioned that genome editing could bring routine genome editing of non-human primates within reach, which could substantially diminish these organisms' welfare and quality of life (81).

Third, it was mentioned that genome editing might decrease the suffering of many species of wild animals, for example, by changing the reproductive behavior of prey animals in ways that reduce their high infant mortality rate (26). It was argued that the harm that would be prevented by doing so would outweigh the harm inflicted on animals during development and testing of these strategies (26). On the other hand, authors argued that scientists cannot be confident enough that this strategy will successfully decrease wild animal suffering given the complexity of ecosystems, the unpredictability of climate change and the indeterminacy of human behavior (139). With regards to reviving extinct species, it was mentioned that these animals could end up suffering as a result of the processes used or because of their genomic variations (12), and that revived species could threaten other animals if they become a vector or reservoir for viruses (112).

Finally, it was argued that genome editing could affect animal welfare in several other ways. Authors noted that genome editing could decrease animal welfare if somatic cell nuclear transfer (SCNT) cloning were used to deliver the nuclease-mediated modifications; SCNT is associated with embryonic losses, postnatal death and birth defects (74,114). Authors also mentioned that genome editing could result in off-target mutations or unintended effects, which could negatively affect animal health (9,20,25,45,111,140). Others argued that genome editing using engineered nucleases could result in fewer off-target effects than previous techniques (9). Furthermore, the so-called non-identity problem was raised in the context of creating genetically modified animals; if these animals have a life worth living, one cannot conclude that they are worse off, even if they have welfare problems, for they would not have existed if they had not been genetically modified (115,134).

With regard to GDTs, it was mentioned that this technology could be a humane method to eliminate invasive species (6). On the other hand, it was argued that such applications could lead humans to ignore the predicament of the animal and to accept negative effects on animal welfare for the sake of other goals (9), although this risk could be prevented by using less drastic GDT designs and using them to promote animal welfare (for instance, by driving disease resistance into wild populations) (9).

Animal dignity and species-specific capacities

Several authors argued that (applications of) genome editing are undesirable not because they might harm the welfare of these animals, but because they might be harmed in other ways. First, it was argued that genome editing instrumentalizes animals by using them as mere objects to serve human purposes (20,54,91,112,115), whereas these animals have intrinsic value (20), and in any case prospective human benefits should not be used to justify harm to animals (54). For particular applications such as reviving extinct species or creating genome-edited pets, authors argued that it could be inappropriate to alter physiological limits (41,56) or to exploit the animals for unimportant human purposes like entertainment (12). Additionally, it was mentioned that genome editing could be viewed as the initiation of increasingly imbalanced power distribution between humans and animals (111). On the other hand, some authors argued that genome editing could prevent additional violations to animal rights, which should be considered preferable to the status quo, even on an account that considers raising animals for human consumption to be impermissible (107).

Second, it was argued that genome editing could be an affront to an animal's dignity (54,113) or could prevent the animal from living according to its instincts (93). On the other hand, it was argued that the Kantian concept of dignity cannot be applied to animals, for it is tied to prerequisite conditions, such as the ability to exert self-determination or to be a moral agent, that animals do not possess (141). Likewise, it was argued that it does not make sense to propose that genome editing could impinge on an animal's dignity and thereby harm that animal even if its welfare is improved, because what is good for an individual must in some way resonate with that individual (107). Similarly, it was argued that dignity-related arguments ultimately cannot justify

an objection that is based on a species norm rather than on respect for individual animals, as is the case in the discussion on enhancement (115,134). Finally, authors noted that because genome editing could determine which individual comes into existence, it could be hard to say that its rights were infringed, its dignity violated, or even that it was wrongly instrumentalized because it would otherwise not exist (136).

Third, it was argued that genome editing could affect the telos (the essence and purpose) of an animal (111) if they are genetically altered to the point where they lose the behavior that makes them that particular animal (137), for example, if genome editing were used to create diminished animals (127). In response, it was argued that the idea that there is a 'true essence' of a species is mistaken, as behaviors and tendencies change over time (107); furthermore, the telos of a creature could still be respected by providing it with an environment that fits its altered genetic predispositions (107). Moreover, it was argued that it could be morally acceptable to modify an animal's telos if the animal was made less miserable or indeed happier because only an individual animal, not its telos, can be harmed (138).

With regard to species-specific considerations, it was argued that genome editing could expedite transgenesis in non-human primates, which likely occupy a level of moral status that would obligate us to protect them from being used in this way (81) or to allow it only in extremely exceptional circumstances (79). It was also mentioned that genome editing could only be rightfully done if its permissibility were evaluated for each species on its own merits (54). With regard to mosquitoes, it was mentioned that using GDTs to drive them to extinction could breach the sanctity of their lives, however, it was argued that neither existing mosquitoes (that will not die nor suffer, but merely fail to reproduce), nor the species holistically (for which it could not be considered clear that they possess relevant cognitive capacities) bear a significant degree of moral status (48).

Finally, objections were made to specific applications of genome editing. It was argued that although genome editing could increase animal welfare by facilitating diminishment, this result would be an inappropriate response to the systematic wronging (136) or inappropriate valuation (123) of agricultural animals, whereas we have a duty of reparation to members of this historically wronged group (136). Authors also mentioned that genome editing could facilitate xenotransplantation, which might be considered ethically untenable because it compromises species boundaries and treats animals as redesignable systems for human use (91). On the other hand, it was argued that species norms (which could also be breached if genome editing were used for animal diminishment) are only indirectly morally significant as a generally useful guide to evaluating animal welfare (134,136). Similarly, it was mentioned that 'disabilities' caused by diminishment, which could affect the species-typical essence of these animals, would not necessarily make these animals worse off, as the literature on human disabilities has taught us (107,135).

(iii) Environment-related reasons

Environmental considerations

Environmental considerations were mostly used to argue against genome editing. One line of argument pursued the potential impacts of genome-edited animals on ecosystems. Authors argued that both genome-edited organisms (25,35) and gene drive organisms (6,7,25,28,31,35,40,41,45,53,78,117,120) could have unknown negative effects on ecosystems. It was mentioned that gene drive organisms could be more transformative, uncontrollable and ecologically damaging than other genome-edited organisms that contain self-limiting genes (30), particularly if GDTs were used to eradicate species (7,25,31,53,78,120). By eradicating a species, GDTs could disrupt the positive contributions of these species in native ecosystems (131), for example, by eliminating the food source of another species (7,78,120) or promoting the proliferation of invasive pests (7,78). By contrast, it was argued that genome editing could enable ecological conservation (45,47) and save endangered native species (5,50,52) if used to eradicate invasive species (5,38,50,52) or revive ecological proxies of extinct species (12,142). It was argued that using GDTs to protect threatened species and reduce invasive species could conserve the natural and cultural world for future generations, possibly rendering its use imperative from an intergenerational justice perspective (45).

Authors also argued that genome editing could impact the environment in other ways. On the one hand, it was reasoned that using genome editing to increase the productivity of livestock could be undesirable given the negative impact of farming on the environment, for example, through greenhouse gas production and water and land pollution (20). On the other hand, genome editing could perhaps contribute to reducing the environmental impact of animal production, for example, by decreasing the amount of phosphate pollution (113). Similarly, authors noted that using GDTs to control agricultural pests could be a more environmentally sound control method than using insecticides (19) and that GDTs could help scientists to develop and support more sustainable agricultural models (5,22,38,39), for example, by editing populations of resistant species to become vulnerable to pesticides and herbicides again (5,22,39).

Authors raised several environmental considerations in response to specific proposed applications of genome editing, in particular reviving extinct species. On the one hand, it was argued that reviving extinct species could be just; because humans caused the extinction and have the power to revive them, they may have a duty to do so (12). On the other hand, it was mentioned that in some cases there may no longer be a niche for a particular revived species (12,112), and as a result the revived species may do substantial environmental damage if it is released or escapes into the environment. Reviving animals could also diminish the desire to protect existing species (12,112). Finally, it was mentioned that genome editing will fail to genuinely recreate species because there would not be a reproductive nor spatiotemporal relationship between the resurrected animal and other members of its species (12,143). In response to the ecological damage that could result from using genome editing to change the reproductive behavior of wild animals to prevent suffering, it was mentioned that such damage could be offset by modifying other features of the ecosystem, too (26).

Finally, it was argued that genome editing could cross moral limits if humans were to use it to breach natural boundaries or to act out of hubris (12,54,115,132), as nature and life should not be completely manufactured or planned and we should acknowledge their unpredictability (12,115). Some authors noted that genome editing might in itself constitute an unnatural interference with nature (115,133). Authors also argued that while the natural order might not hold an intrinsic moral value, deleting genetic diversity risks eliminating advantageous traits (22). In response, authors noted that it is unclear what is meant by 'naturalness' (93,107). Furthermore, the natural is not necessarily good and the unnatural is not necessarily bad (93,107). Similarly, it was argued that although it could be said that using genome editing could amount to 'playing God' or displaying hubris, there may be sufficient reasons—such as saving many lives—to justify improving the given (48). For GDTs, it was mentioned that the use of this technology to control certain invasive species, if successful, could become a Trojan horse to legitimize the eradication of other species without questioning to whom or what they are harmful (40).

Discussion

To the best of our knowledge, this review constitutes the first systematic review of reasons for and against development and use of new-generation genome editing technologies in non-human animals as reported in the academic literature. Our review shows that a wide and diverse range of reasons is brought forward and provides a descriptive overview of these reasons, offering a starting point for subsequent further research and normative analysis (16).

Importantly, many arguments mentioned in this review are not reasons for or against all uses of genome editing in animals. Instead, they point to possible conditions for the responsible use of these technologies. For example, the fact that genetically modified mosquitoes could potentially cause negative consequences by spreading the modified gene beyond the target population, could lead to the requirement that, among other conditions, a first trial site be geographically isolated, such as an island (51). Our review also underlines that different ethical considerations apply to different applications of genome editing in animals. From this point of view, the question is not whether genome editing in animals is ethically acceptable, but whether there are conditions under which it can be ethically employed.

In what follows, we make four additional observations about the academic debate, and suggest areas for future research and analysis. In particular, we note a low disciplinary diversity in the authors shaping the academic debate, a scarcity of systematic comparisons of potential consequences of using these technologies, underrepresented or missing concerns, especially regarding animal interests, and a disjunction between the public and academic debate on this topic. We elaborate on these observations below.

The academic literature lacks disciplinary diversity

Our findings provide insight into who is shaping the academic debate on the use of gene editing technologies in non-human animals. As table 1 illustrates, while authors from different backgrounds are involved in this debate, the large majority are (mostly biomedical or veterinary) scientists, investigating the technical feasibility of different applications of genome editing in animals. On the one hand, a concern for ethics on the part of scientists is important and encouraging. On the other hand, it shows that authors working in ethics, philosophy and the social sciences are underrepresented. This low disciplinary diversity is particularly problematic as the debate moves from discussions of technical feasibility to (potential) real-world applications, in which academic experts will likely influence policy and regulatory decisions (14,144). To critically assess the applications of genome editing in animals from different perspectives, interdisciplinary and proactive evaluation of the technologies and their ethical and societal implications — for example, through ethics parallel research (145,146) — is essential. Ethics parallel research entails an ethical evaluation of emerging technologies in parallel with—or even in advance of—the developing science, allowing scientists and ethicists to co-shape innovation processes and governance in an ethically sound way during the development of the technology (145).

Few articles include systematic comparisons

Our findings also illuminate the characteristics of the specific reasons addressed in the literature. While many reasons related to potential harms and benefits, surprisingly few articles engaged in a systematic comparison of the harms and benefits of the proposed application of genome editing compared to alternatives. This is noteworthy, as such systematic comparisons are necessary to draw conclusions about what would result in the best overall consequences. Such an analysis could draw on the principles of proportionality and subsidiarity. According to the principle of proportionality, potential benefits should be balanced against potential harms or risks; those that argue in favor of or against (applications of) genome editing in animals ought to present an explicit comprehensive overview of the benefits, harms and risks in question and argue why the harms outweigh the benefits or vice versa. The principle of subsidiarity entails that a policy should only be adopted if there is no less harmful policy that would achieve the same result. This principle suggests that applications of genome editing ought to be compared to alternative policies in terms of potential harms and benefits, including the – often forgotten – benefits and harms of the status quo, including the costs of inaction. In the case of GDTs, for example, potential ecological damage resulting from their use is a pressing concern, warranting a thorough inventory of related risks and harms. When weighing those, the principle of subsidiarity requires us – among other things – to balance the possible ecological damage of using GDTs to eradicate vector-borne diseases with the deaths that are now caused by these diseases and the ecological damage of using pesticides. This kind of analysis is consistent with calls from the scientific community to integrate comparative assessment of harms, risks and benefits into the regulatory framework (147,148). Yet where some scientific reports define benefits in narrow economic terms, the principle of subsidiarity requires a broad definition of and metric for benefits.

Underrepresented or missing concerns

Given that this review concerns genome editing in animals, it is remarkable how few animal-related reasons have been put forward; most reasons for or against the use of genome editing in animals rest on human-related grounds. Little of the biomedical literature considered the welfare of (research) animals; for example, articles that mentioned off-target effects seldom considered whether these effects could have an impact on animal welfare. Similarly, there was relatively little reflection on species-specific considerations. Although the moral status and interests of non-human primates were brought up (41,79,81), the moral status of other animals was rarely mentioned. Given that accounts of moral status are generally founded in sentience (149) and consciousness, the interests of other animals appear worthy of more attention within this debate.

On a related note, while the relationship between humans and animals was brought up in several reasons, particularly those related to animal dignity, this relationship was never framed in terms of human virtues (150). Such an analysis might ask, for example, who we become when we use and alter animals in certain ways. Indeed, when it comes to ethical theory, we note that the most frequently reported reasons—to a large extent originating from biomedical literature—were consequentialist in nature, i.e. focusing on potential (positive or negative) outcomes of using genome editing technology in animals for human health, animal welfare or ecosystems. While an initial emphasis on consequentialism is consistent with general argumentative patterns around new and emerging science and technologies (151), other ethical theories are relevant to this debate and will also be necessary to understand and engage with public attitudes and concerns.

Disjunction between the expert and public debate

Academic experts have made significant calls for public engagement with and debate about genome editing (4,35,100,152–154), particularly with regard to the possible use of GDTs (5,6,33,39,40,43,120,130). A study commissioned by the United Kingdom's Royal Society explores public perceptions and the reasoning behind them (154). In both this study and the academic debate more generally, considerable weight is given to the potential for genetically modified animals to improve human health or (negatively) impact ecosystems (154). However, other public concerns regarding genome editing technologies are thus far underrepresented in the academic literature, including the public concern for equity of access to the potential benefits of genome editing technologies, questions about the just distribution of governmental funding of genome editing compared with other investments, and concerns about the commercialization of genome editing technologies. With regard to commercialization, members of the public have raised the worry that businesses could prioritize profit-making over the public good and could fail to provide a balanced representation of the benefits and risks of these technologies (154). The fact that these concerns are largely absent from the academic debate on genome editing in animals is particularly significant given ongoing calls for public engagement and raises interesting questions that relate to a broader discussion about what the rationale, form and aim of public engagement should be. If the goals of such engagement are not merely to inform the public, but also to address societal challenges and to allow the public to be involved in shaping technological developments together with other stakeholders, then issues regarding commercialization, distributive justice and access to the benefits of genome editing technologies are worthy of more attention in the academic literature.

Limitations

This systematic review provides a comprehensive overview of the reasons brought forward in the academic debate on genome editing in animals. The articles presented were included after a thorough screening of the academic literature on the topic by two independent reviewers, based on a search strategy that was guided by experienced librarians. Nonetheless, this review has several limitations.

First, given the focus on relatively new genome editing technologies and a large amount of literature on this topic, this review included articles published between 2010 and 2018. We recognize that arguments raised previously, in different contexts or in older but related debates, may be relevant for the current discussion of genome editing. Second, a systematic review of this kind always involves reporting bias; a different group of researchers could have selected or grouped the included reasons in a different way. Third, we could not systematically perform a quality assessment of the included literature, as there is no screening instrument to assess the quality of normative papers or the reasons mentioned. Finally, we note that it was beyond the scope of this paper to assess the scientific validity of the reasons and different applications of genome editing discussed in the included articles.

Conclusion

Genome editing has a broad range of possible applications in research animals, farm animals and wild animals. Despite an ongoing academic debate on this topic, this study is the first comprehensive overview of this debate. Our article provides a systematic review of the reasons for and against the development and use of genome editing technologies in animals as reported in the academic literature. We identified 67 different reasons for and 48 different reasons against genome editing in animals, which related to human health, efficiency, risks and uncertainty, animal welfare, animal dignity, environmental considerations and public acceptability. Our findings illuminate several key features of the academic debate thus far, including a low disciplinary diversity in the contributing professionals, a scarcity of systematic comparisons of potential consequences of using these technologies, an underrepresentation of animal interests, and a disjunction between the public and academic debate on this topic.

As such, our article can be considered a call for professionals from a wide range of disciplines to become involved in the academic discussion about genome editing in non-human animals. We also suggest that this ongoing debate seek to incorporate animal interests, systematically compare applications of these technologies using the principles of proportionality and subsidiarity, and further research the range of concerns uncovered through public engagement. Proactive and interdisciplinary collaboration can both advance these technological developments and the academic discourse about them, allowing us to go beyond rhetoric of promises or fears and positioning their ethical analysis in real-world practices (145,155).

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2

Appendix 1: Search strategy systematic review of reasons

Search strategy for Pubmed/MEDLINE:

	Search string	# results
Genome editing	"Genetic Engineering"[Mesh] OR "Clustered Regularly Interspaced Short Palindromic Repeats"[Mesh] OR "CRISPR-cas Systems"[Mesh] OR "Zinc fingers"[Mesh] OR "Transcription Activator-Like Effector Nucleases"[Mesh] OR ((Gene[tiab] OR genetic[tiab] OR genome[tiab]) AND (Engineering[tiab] OR edit[tiab] OR editing[tiab] OR enhancing[tiab] OR enhancement[tiab] OR modification[tiab] OR therapy[tiab])) OR "Zinc finger"[tiab] OR "Zinc fingers"[tiab] OR meganucleases[tiab] OR TALEN[tiab] OR "Transcription Activator-Like Effector Nucleases"[tiab] OR "Transcription Activator Like Effector Nucleases"[tiab] OR "Clustered Regularly Interspaced Short Palindromic Repeats"[tiab] OR "CRISPR"[tiab] OR gene drive" [tiab] OR "gene drives"[tiab]	374.748
Animals*	(Animals[MeSH] NOT (humans[mh] NOT animals[mh:noexp])) OR "Animal experimentation"[MeSH] OR "models, animal"[MeSH] OR "animal population groups"[MeSH] OR ((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR pan[Tiab] OR paniscus[Tiab] OR "pan paniscus"[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR troglodytes[Tiab] OR "pan troglodytes"[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimians[Tiab] OR "bush baby"[Tiab] OR prosimian[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae[Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR pongo[Tiab] OR pygmaeus[Tiab] OR "pongo pygmaeus"[Tiab] OR orangutans[Tiab] OR pygmaeus[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR pongo[Tiab] OR equus[Tiab] OR cow[Tiab] OR calf[Tiab] OR bull[Tiab] OR chicken[Tiab] OR chickens[Tiab] OR gallus[Tiab] OR quail[Tiab] OR bird[Tiab] OR birds[Tiab] OR quails[Tiab] OR poultry[Tiab] OR poultries[Tiab] OR fowl[Tiab] OR fowls[Tiab] OR reptile[Tiab] OR reptilia[Tiab] OR reptiles[Tiab] OR snakes[Tiab] OR snake[Tiab] OR lizard[Tiab] OR lizards[Tiab] OR alligator[Tiab] OR alligators[Tiab] OR crocodile[Tiab] OR crocodiles[Tiab] OR turtle[Tiab] OR turtles[Tiab] OR amphibian[Tiab] OR amphibians[Tiab] OR amphibia[Tiab] OR frog[Tiab] OR frogs[Tiab] OR bombina[Tiab] OR salientia[Tiab] OR toad[Tiab] OR toads[Tiab] OR "epidalea calamita"[Tiab] OR salamander[Tiab] OR salamanders[Tiab] OR eel[Tiab] OR eels[Tiab] OR fish[Tiab] OR fishes[Tiab] OR pisces[Tiab] OR catfish[Tiab] OR catfishes[Tiab] OR siluriformes[Tiab] OR arius[Tiab] OR heteropneustes[Tiab] OR sheatfish[Tiab] OR perch[Tiab] OR perches[Tiab] OR percidae[Tiab] OR perca[Tiab] OR trout[Tiab] OR trouts[Tiab] OR char[Tiab] OR chars[Tiab] OR salvelinus[Tiab] OR "fathead minnow"[Tiab] OR minnow[Tiab] OR cyprinidae[Tiab] OR carps[Tiab] OR carp[Tiab] OR zebrafish[Tiab] OR zebrafishes[Tiab] OR goldfish[Tiab] OR goldfishes[Tiab] OR guppy[Tiab] OR guppies[Tiab] OR chub[Tiab] OR chubs[Tiab] OR tinca[Tiab] OR barbels[Tiab] OR barbus[Tiab] OR pimephales[Tiab] OR promelas[Tiab] OR "poecilia reticulata"[Tiab] OR mullet[Tiab] OR mullets[Tiab] OR seahorse[Tiab] OR seahorses[Tiab] OR mugil curema[Tiab] OR atlantic cod[Tiab] OR shark[Tiab] OR sharks[Tiab] OR catshark[Tiab] OR anguilla[Tiab] OR salmonid[Tiab] OR salmonids[Tiab] OR whitefish[Tiab] OR whitefishes[Tiab] OR salmon[Tiab] OR salmons[Tiab] OR sole[Tiab] OR solea[Tiab] OR "sea lamprey"[Tiab] OR lamprey[Tiab] OR lampreys[Tiab] OR pumpkinseed[Tiab] OR sunfish[Tiab] OR sunfishes[Tiab] OR tilapia[Tiab] OR tilapias[Tiab] OR turbot[Tiab] OR turbots[Tiab] OR flatfish[Tiab] OR flatfishes[Tiab] OR sciuridae[Tiab] OR squirrel[Tiab] OR squirrels[Tiab] OR chipmunk[Tiab] OR chipmunks[Tiab] OR suslik[Tiab] OR susliks[Tiab] OR vole[Tiab] OR voles[Tiab] OR lemming[Tiab] OR lemmings[Tiab] OR muskrat[Tiab] OR	6.856.194

Continued

	Search string	# results
	lemmus[Tiab] OR otter[Tiab] OR otters[Tiab] OR marten[Tiab] OR martens[Tiab] OR martes[Tiab] OR weasel[Tiab] OR badger[Tiab] OR badgers[Tiab] OR ermine[Tiab] OR mink[Tiab] OR minks[Tiab] OR sable[Tiab] OR sables[Tiab] OR gulo[Tiab] OR gulos[Tiab] OR wolverine[Tiab] OR wolverines[Tiab] OR minks[Tiab] OR mustela[Tiab] OR llama[Tiab] OR llamas[Tiab] OR alpaca[Tiab] OR alpacas[Tiab] OR camelid[Tiab] OR camelids[Tiab] OR guanaco[Tiab] OR guanacos[Tiab] OR chiroptera[Tiab] OR chiropteras[Tiab] OR bat[Tiab] OR bats[Tiab] OR fox[Tiab] OR foxes[Tiab] OR iguana[Tiab] OR iguanas[Tiab] OR xenopus laevis[Tiab] OR parakeet[Tiab] OR parakeets[Tiab] OR parrot[Tiab] OR parrots[Tiab] OR donkey[Tiab] OR donkeys[Tiab] OR mule[Tiab] OR mules[Tiab] OR zebra[Tiab] OR zebras[Tiab] OR shrew[Tiab] OR shrews[Tiab] OR bison[Tiab] OR bisons[Tiab] OR buffalo[Tiab] OR buffaloes[Tiab] OR deer[Tiab] OR deers[Tiab] OR bear[Tiab] OR bears[Tiab] OR panda[Tiab] OR pandas[Tiab] OR "wild hog"[Tiab] OR "wild boar"[Tiab] OR fitchew[Tiab] OR fitch[Tiab] OR beaver[Tiab] OR beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) OR wildlife [tiab] OR cattle [tiab] OR livestock [tiab] OR bovine[tiab]	
Ethics	Ethics [Mesh] OR ethics [Subheading] OR ethic [tiab] OR ethics [tiab] OR ethical [tiab] OR moral [tiab]	222.713
Combined	Genome editing AND animals AND ethics	1004
	Language: English and Dutch Publication dates: 01-01-1996 - now	**779**

Search strategy for Web of Science

	Search string	# results
Genome editing	(TS=(Gene OR genetic OR genome)) AND (TS=(Engineering OR edit OR editing OR enhancing OR enhancement OR modification OR therapy)) OR TS=("Zinc finger" OR "Zinc fingers" OR meganucleases OR TALEN OR "Transcription Activator-Like Effector Nucleases" OR "Transcription Activator Like Effector Nucleases" OR "Clustered Regularly Interspaced Short Palindromic Repeats" OR "CRISPR" OR "gene drive" OR "gene drives")	569.256
Animals*	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR wildlife OR cattle OR livestock OR bovine) amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR "mugil curema" OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR	6.718.031

Continued

	Search string	*# results*
Ethics	TS=(ethics OR ethic OR ethical OR moral)	227.559
Combined	Genome editing AND animals AND ethics	616
	Language: English and Dutch Publication dates: 01-01-1996 - now	**539**

Search strategy for Scopus

	Search string	*# results*
Genome editing	(TITLE-ABS-KEY(Gene OR genetic OR genome)) AND TITLE-ABS-KEY (Engineering OR edit OR editing OR enhancing OR enhancement OR modification OR therapy) OR TITLE-ABS-KEY ("Zinc finger" OR "Zinc fingers" OR meganucleases OR TALEN OR "Transcription Activator-Like Effector Nucleases" OR "Transcription Activator Like Effector Nucleases" OR "Clustered Regularly Interspaced Short Palindromic Repeats" OR "CRISPR" OR "gene drive" OR "gene drives")	702.254
Animals*	TITLE-ABS-KEY (animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR "bush babies" OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR "fathead minnow" OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR "poecilia reticulata" OR mullet OR mullets OR seahorse OR seahorses OR "mugil curema" OR "atlantic cod" OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR "sea lamprey" OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR "xenopus laevis" OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras OR wildlife OR cattle OR livestock OR bovine)	9.265.556
Ethics	TITLE-ABS-KEY(ethics OR ethic OR ethical OR moral)	417.193
Combined	Genome editing AND animals AND ethics	1741
Exclusion MEDLINE	**AND NOT index(medline);** Language: English and Dutch; Publication dates: 01-01-1996 - now	**405**

Search strategy for CAB Abstracts

Search string for	*Search string*	*# results*
Genome editing	Exp genetic engineering/ or gene therapy/ or transgenic animals/ OR ((Gene.ti,ab OR genetic.ti,ab OR genome.ti,ab) AND (Engineering.ti,ab OR edit.ti,ab OR editing.ti,ab OR enhancing.ti,ab OR enhancement.ti,ab OR modification.ti,ab OR therapy.ti,ab)) OR Zinc finger.ti,ab OR Zinc fingers.ti,ab OR meganucleases.ti,ab OR TALEN.ti,ab OR Transcription Activator-Like Effector Nucleases.ti,ab OR Transcription Activator Like Effector Nucleases.ti,ab OR Clustered Regularly Interspaced Short Palindromic Repeats.ti,ab OR CRISPR.ti,ab OR gene drive.ti,ab OR gene drives.ti,ab.	90.189
Ethics	Exp ethics/ or moral values/ or ethics.ti,ab or ethics.ti,ab or ethical.ti,ab or moral.ti,ab	17.827
Combined	Genome editing AND ethics	843
	Language: English and Dutch Publication dates: 01-01-1996 - now	**578**

Search strategy for Philosopher's Index

	Search string	*# results*
Genome editing	((Gene.ti,ab OR genetic.ti,ab OR genome.ti,ab) AND (Engineering.ti,ab OR edit.ti,ab OR editing.ti,ab OR enhancing.ti,ab OR enhancement.ti,ab OR modification.ti,ab OR therapy.ti,ab)) OR Zinc finger.ti,ab OR Zinc fingers.ti,ab OR meganucleases.ti,ab OR TALEN.ti,ab OR Transcription Activator-Like Effector Nucleases.ti,ab OR Transcription Activator Like Effector Nucleases.ti,ab OR Clustered Regularly Interspaced Short Palindromic Repeats.ti,ab OR CRISPR.ti,ab OR gene drive .ti,ab OR gene drives.ti,ab	703
Animals*	animals.ti,ab OR animal.ti,ab OR mice.ti,ab OR mus.ti,ab OR mouse.ti,ab OR murine.ti,ab OR woodmouse.ti,ab OR rats.ti,ab OR rat.ti,ab OR murinae.ti,ab OR muridae.ti,ab OR cottonrat.ti,ab OR cottonrats.ti,ab OR hamster.ti,ab OR hamsters.ti,ab OR cricetinae.ti,ab OR rodentia.ti,ab OR rodent.ti,ab OR rodents.ti,ab OR pigs.ti,ab OR pig.ti,ab OR swine.ti,ab OR swines.ti,ab OR piglets.ti,ab OR piglet.ti,ab OR boar.ti,ab OR boars.ti,ab OR "sus scrofa".ti,ab OR ferrets.ti,ab OR ferret.ti,ab OR polecat.ti,ab OR polecats.ti,ab OR "mustela putorius".ti,ab OR "guinea pigs".ti,ab OR "guinea pig".ti,ab OR cavia.ti,ab OR callithrix.ti,ab OR marmoset.ti,ab OR marmosets.ti,ab OR cebuella.ti,ab OR hapale.ti,ab OR octodon.ti,ab OR chinchilla.ti,ab OR chinchillas.ti,ab OR gerbillinae.ti,ab OR gerbil.ti,ab OR gerbils.ti,ab OR jird.ti,ab OR jirds.ti,ab OR merione.ti,ab OR meriones.ti,ab OR rabbits.ti,ab OR rabbit.ti,ab OR hares.ti,ab OR hare.ti,ab OR diptera.ti,ab OR flies.ti,ab OR fly.ti,ab OR dipteral.ti,ab OR drosphila.ti,ab OR drosophilidae.ti,ab OR cats.ti,ab OR cat.ti,ab OR carus.ti,ab OR felis.ti,ab OR nematoda.ti,ab OR nematode.ti,ab OR nematoda.ti,ab OR nematode.ti,ab OR nematodes.ti,ab OR sipunculida.ti,ab OR dogs.ti,ab OR dog.ti,ab OR canine.ti,ab OR canines.ti,ab OR canis.ti,ab OR sheep.ti,ab OR sheeps.ti,ab OR mouflon.ti,ab OR mouflons.ti,ab OR ovis.ti,ab OR goats.ti,ab OR goat.ti,ab OR capra.ti,ab OR capras.ti,ab OR rupicapra.ti,ab OR chamois.ti,ab OR haplorhini.ti,ab OR monkey.ti,ab OR monkeys.ti,ab OR anthropoidea.ti,ab OR anthropoids.ti,ab OR saguinus.ti,ab OR tamarin.ti,ab OR tamarins.ti,ab OR leontopithecus.ti,ab OR hominidae.ti,ab OR ape.ti,ab OR apes.ti,ab OR pan.ti,ab OR paniscus.ti,ab OR "pan paniscus".ti,ab OR bonobo.ti,ab OR bonobos.ti,ab OR troglodytes.ti,ab OR "pan troglodytes".ti,ab OR gibbon.ti,ab OR gibbons.ti,ab OR siamang.ti,ab OR siamangs.ti,ab OR nomascus.ti,ab OR symphalangus.ti,ab OR chimpanzee.ti,ab OR chimpanzees.ti,ab OR prosimians.ti,ab OR "bush baby".ti,ab OR prosimian.ti,ab OR bush babies.ti,ab OR galagos.ti,ab OR galago.ti,ab OR pongidae.ti,ab OR gorilla.ti,ab OR gorillas.ti,ab OR pongo.ti,ab OR pygmaeus.ti,ab OR "pongo pygmaeus".ti,ab OR orangutans.ti,ab OR pygmaeus.ti,ab OR lemur.ti,ab OR lemurs.ti,ab OR lemuridae.ti,ab OR horse.ti,ab OR horses.ti,ab OR pongo.ti,ab OR equus.ti,ab OR cow.ti,ab OR calf.ti,ab OR bull.ti,ab OR chicken.ti,ab OR chickens.ti,ab OR gallus.ti,ab OR quail.ti,ab OR bird.ti,ab OR birds.ti,ab OR quails.ti,ab OR poultry.ti,ab OR poultries.ti,ab OR fowl.ti,ab OR fowls.ti,ab OR reptile.ti,ab OR reptilia.ti,ab OR reptiles.ti,ab OR snakes.ti,ab OR snake.ti,ab OR lizard.ti,ab OR lizards.ti,ab OR alligator.ti,ab OR alligators.ti,ab OR crocodile.ti,ab OR crocodiles.ti,ab OR turtle.ti,ab OR turtles.ti,ab OR amphibian.ti,ab OR amphibians.ti,ab OR amphibia.ti,ab OR frog.ti,ab OR frogs.ti,ab OR bombina.ti,ab OR salientia.ti,ab OR toad.ti,ab OR toads.ti,ab OR "epidalea calamita".ti,ab OR salamander.ti,ab OR salamanders.ti,ab OR eel.ti,ab OR eels.ti,ab OR fish.ti,ab OR fishes.ti,ab OR pisces.ti,ab OR catfish.ti,ab OR catfishes.ti,ab OR siluriformes.ti,ab OR arius.ti,ab OR heteropneustes.ti,ab OR sheatfish.ti,ab OR perch.ti,ab OR perches.ti,ab OR percidae.ti,ab OR perca.ti,ab OR trout.ti,ab OR trouts.ti,ab OR char.ti,ab OR chars.ti,ab OR salvelinus.ti,ab OR "fathead minnow".ti,ab OR minnow.ti,ab OR cyprinidae.ti,ab OR carps.ti,ab OR carp.ti,ab OR zebrafish.ti,ab OR zebrafishes.ti,ab OR goldfish.ti,ab OR goldfishes.ti,ab OR guppy.ti,ab OR guppies.ti,ab OR chub.ti,ab OR chubs.ti,ab OR tinca.ti,ab OR barbels.	12.676

Continued

	Search string	*# results*
	ti,ab OR barbus.ti,ab OR pimephales.ti,ab OR promelas.ti,ab OR "poecilia reticulata".ti,ab OR mullet.ti,ab OR mullets.ti,ab OR seahorse.ti,ab OR seahorses.ti,ab OR mugil curema.ti,ab OR atlantic cod.ti,ab OR shark.ti,ab OR sharks.ti,ab OR catshark.ti,ab OR anguilla.ti,ab OR salmonid.ti,ab OR salmonids.ti,ab OR whitefish.ti,ab OR whitefishes.ti,ab OR salmon.ti,ab OR salmons.ti,ab OR sole.ti,ab OR solea.ti,ab OR "sea lamprey".ti,ab OR lamprey.ti,ab OR lampreys.ti,ab OR pumpkinseed.ti,ab OR sunfish.ti,ab OR sunfishes.ti,ab OR tilapia.ti,ab OR tilapias.ti,ab OR turbot.ti,ab OR turbots.ti,ab OR flatfish.ti,ab OR flatfishes.ti,ab OR sciuridae.ti,ab OR squirrel.ti,ab OR squirrels.ti,ab OR chipmunk.ti,ab OR chipmunks.ti,ab OR suslik.ti,ab OR susliks.ti,ab OR vole.ti,ab OR voles.ti,ab OR lemming.ti,ab OR lemmings.ti,ab OR muskrat.ti,ab OR muskrats.ti,ab OR lemmus.ti,ab OR otter.ti,ab OR otters.ti,ab OR marten.ti,ab OR martens.ti,ab OR martes.ti,ab OR weasel.ti,ab OR badger.ti,ab OR badgers.ti,ab OR ermine.ti,ab OR mink.ti,ab OR minks.ti,ab OR sable.ti,ab OR sables.ti,ab OR gulo.ti,ab OR gulos.ti,ab OR wolverine.ti,ab OR wolverines.ti,ab OR minks.ti,ab OR mustela.ti,ab OR llama.ti,ab OR llamas.ti,ab OR alpaca.ti,ab OR alpacas.ti,ab OR camelid.ti,ab OR camelids.ti,ab OR guanaco.ti,ab OR guanacos.ti,ab OR chiroptera.ti,ab OR chiropteras.ti,ab OR bat.ti,ab OR bats.ti,ab OR fox.ti,ab OR foxes.ti,ab OR iguana.ti,ab OR iguanas.ti,ab OR xenopus laevis.ti,ab OR parakeet.ti,ab OR parakeets.ti,ab OR parrot.ti,ab OR parrots.ti,ab OR donkey.ti,ab OR donkeys.ti,ab OR mule.ti,ab OR mules.ti,ab OR zebra.ti,ab OR zebras.ti,ab OR shrew.ti,ab OR shrews.ti,ab OR bison.ti,ab OR bisons.ti,ab OR buffalo.ti,ab OR buffaloes.ti,ab OR deer.ti,ab OR deers.ti,ab OR bear.ti,ab OR bears.ti,ab OR panda.ti,ab OR pandas.ti,ab OR "wild hog".ti,ab OR "wild boar".ti,ab OR fitchew.ti,ab OR fitch.ti,ab OR beaver.ti,ab OR beavers.ti,ab OR jerboa.ti,ab OR jerboas.ti,ab OR capybara.ti,ab OR capybaras.ti,ab OR wildlife.ti,ab OR cattle.ti,ab OR livestock.ti,ab OR bovine.ti,ab	
Combined	Genome editing AND animals	76
	Language: English and Dutch Publication dates: 01-01-1996 - now	**58**

***** The search string for 'animals' was adapted from Hooijmans, Tillema, Leenaars & Ritskes-Hoitinga (2010).

Appendix 2: Data extraction sheet systematic review of reasons

General information
Authors, country & background author
Full reference
Which technology?
Which application?
Scope? *E.g. only animals / also other species (plants/humans) mentioned in the paper?* *If only animals, specific animals mentioned?*
Aim(s)/general conclusion drawn

Data extraction			
Reasons mentioned	**Page no.**	**Theme**	**Other comments**
1. ...			
2. ...			
Etc. ...			

3

EXPERTS' MORAL VIEWS ON GENE DRIVE TECHNOLOGIES: A QUALITATIVE INTERVIEW STUDY

Nienke de Graeff
Karin R. Jongsma
Annelien L. Bredenoord

BMC Medical Ethics. 2021; 22, 1-15.

Abstract

Background

Gene drive technologies (GDTs) promote the rapid spread of a particular genetic element within a population of non-human organisms. Potential applications of GDTs include the control of insect vectors, invasive species, and agricultural pests. Whether, and if so, under what conditions, GDTs should be deployed is hotly debated. Although broad stances in this debate have been described, the convictions that inform the moral views of the experts shaping these technologies and related policies have not been examined in depth in the academic literature.

Methods

In this qualitative study, we interviewed GDT experts (n = 33) from different disciplines to identify and better understand their moral views regarding these technologies. The pseudonymized transcripts were analyzed thematically.

Results

The respondents' moral views were principally influenced by their attitudes towards (1) the uncertainty related to GDTs; (2) the alternatives to which they should be compared; and (3) the role humans should have in nature. Respondents agreed there is epistemic uncertainty related to GDTs, identified similar knowledge gaps, and stressed the importance of realistic expectations in discussions on GDTs. They disagreed about whether uncertainty provides a rationale to refrain from field trials ('risks of intervention' stance) or to proceed with phased testing to obtain more knowledge given the harms of the status quo ('risks of non-intervention' stance). With regards to alternatives to tackle vector-borne diseases, invasive species and agricultural pests, respondents disagreed about which alternatives should be considered (un)feasible and (in)sufficiently explored: conventional strategies ('downstream solutions' stance) or systematic changes to health care, political and agricultural systems ('upstream solutions' stance). Finally, respondents held different views on nature and whether the use of GDTs is compatible with humans' role in nature ('interference' stance) or not ('non-interference stance').

Conclusions

This interview study helps to disentangle the debate on GDTs by providing a better understanding of the moral views of GDT experts. The obtained insights provide valuable stepping-stones for a constructive debate about underlying value conflicts and call attention to topics that deserve further (normative) reflection. Further evaluation of these issues can facilitate the debate on and responsible development of GDTs.

Background

Gene drive technologies (GDTs) promote the rapid, progressive spread of a particular genetic element within a population of non-human organisms. Whereas a given gene is passed on to approximately half of an organism's offspring in normal Mendelian inheritance, gene drives can promote the biased inheritance of a particular gene, so that this gene is passed on to most or even all of an organism's offspring[8]. If organisms reproduce quickly, the edited trait can consequently spread rapidly and permanently across the population (1). In the past few years, GDTs have advanced substantially, from a largely theoretical proposal to proof-of-concept experiments in various organisms (2,3). While a number of natural and synthetic gene drive systems based on different molecular mechanisms exist (4), the gene-editing tool CRISPR-Cas9 (Clustered Regularly Interspaced Palindromic Repeats-CRISPR-associated protein 9) has led to particularly significant advancements in GDTs (2). Gene drives are now "on the horizon" (1) .

GDTs have been proposed as a potential strategy to address several major problems, including the burden of vector-borne diseases such as malaria (5), the agricultural, economic, and environmental damage caused by invasive species (6), and the rise of pesticide and herbicide resistance in agricultural settings (7). Additionally, GDTs could be used in basic research, for example to construct animal models of human disease (8). Various types of gene drive designs have been proposed, ranging from self-sustaining gene drives which are designed to spread throughout all populations of a species, to self-limiting or thresholded gene drives that are spatially or temporally limited in their spread (1).

The development and possible use of GDTs has stirred considerable scholarly debate. Major concerns in this debate relate to biosafety and biosecurity issues, including the safeguarding of laboratory experiments with GDTs and potential negative effects on ecosystems due to unintended consequences or misuse of the technology (9,10). Several papers have mapped the 'ethical landscape' and explored various ethical aspects related to GDTs (11,12). Other authors have analyzed specific concerns with regard to these technologies, including objections pertaining to 'playing God' and the presumed intrinsic wrongness of tampering with nature (13), intergenerational equity issues (14) and issues related to decision-making about these technologies (15–17). Finally, various guidelines (1,18–21), consensus statements and workshop reports (22–27) on the scientific, ethical, social, legal and policy implications of GDTs have been published.

A key question in the debate on GDTs is whether – and if so, under what conditions – GDTs should be deployed, with different organizations and stakeholders taking

8 If organisms have an inheritance pattern that can be biased, typically meaning that they can reproduce sexually (68).

3

diverging stances. On one side of the spectrum, parties stress the potential of GDTs and argue this provides a strong argument to develop these technologies. These organizations and stakeholders mostly advocate a phased testing approach in which GDTs are investigated in a step-wise manner: first in laboratory studies, then in small-scale, confined field experiments, followed by open small-scale releases and finally large-scale field releases (1,18,26). On the other side of the spectrum, others contend these technologies are too risky or ethically impermissible on other grounds, and argue in favor of a moratorium on field applications of GDTs (28–30). Whilst the stances of particular organizations and stakeholders (3,22,31,32) as well as a range of ethical and governance issues related to GDTs (1,11–17,25) have been identified and described in the literature, the convictions that inform the stances of a wide range of GDT experts have not yet been examined in depth.

Qualitative interviews are a valuable method to identify, better understand, and juxtapose people's moral views; they can improve the understanding of ethical implications of a technology by providing insights into how interviewees view and weigh different ethical aspects (33). In this study, we therefore aimed to investigate the moral views of gene drive experts working in various disciplines through a qualitative interview study. We considered it particularly relevant to study the moral views of experts that are actively involved in (the debate on) GDTs, as they are likely to shape these technologies and influence related policymaking. Technological development and related policymaking are human processes; they are not neutral, but rather influenced by the attitudes, convictions and values of those that shape these technologies and the debates about them (34,35). By providing insight into the moral views of gene drive experts and linking our results to the previously published literature, this analysis intends to facilitate a more informed and reflected debate on these disputed technologies, and in turn hopes to contribute to their responsible development.

Methods

We performed a qualitative interview study to investigate the moral views of gene drive experts from a variety of disciplines. The study is reported in accordance with the consolidated criteria for reporting qualitative studies (COREQ) (36).

Participant selection and recruitment

Professionals were considered eligible for inclusion in the study if they had contributed to academic publications and/or policy documents on GDT research and development. Eligible participants were identified through a review of the academic (9) and policy publications on GDTs and through so-called snowball sampling, i.e. based on recommendations by previous participants (37). Based on such snowball sampling, three professionals with broader expertise on respectively global research ethics, anthrozoology (human-non-human-animal studies), and the ethics of gene-editing technologies were also included given the relevance of these fields for the debate on GDTs. To capture a wide range of perspectives on GDTs, a variety of experts from different professional backgrounds and countries were identified. Potential participants were approached and informed about the set-up of the study by e-mail by NG. Recruitment was ended when saturation was reached, i.e. when subsequent interviews no longer brought up new issues ('coding saturation') and the formulated themes were sufficiently understood ('meaning saturation') (38).

Data collection

Semi-structured interviews were conducted by NG (trained qualitative researcher, female, MA, MD, PhD candidate). In 28 out of 33 interviews, there had been no previous contact between the interviewer and the participant beforehand; in 5 out of the 33 interviews, the interviewer and the participant had met each other prior to the interview in research meetings or a research visit. The interview guide for the interviews (see Appendix) was based on an analysis of the ethical arguments related to GDTs that were identified in a previous review (9) and in discussions amongst the research team. The interview consisted of open-ended questions related to potential benefits, hazards and risks of GDTs, stakeholder involvement and governance of GDTs.

This article reports the interview findings related to what may be classified as the substantive ethical questions, concerns, and implications of GDTs, i.e. those questions, concerns, and implications that relate to "what is right in terms of duties, rights, and values (..) independent of any decision-making procedure" (39) (p. 155)[9]. The semi-structured design of the study ensured consistency in a number of topics to be discussed by all participants, while also allowing participants to bring up or emphasize particular new issues they considered relevant. Interviews were conducted in English or Dutch and either took place at a location chosen by the participant (for 25 of the 33 interviews), or online via a video conferencing platform (for 8 interviews). An intern (female biomedical science student, BSc) listened to 3 interviews. The interviews were audiotaped, transcribed verbatim, and pseudonymized.

Data analysis

The pseudonymized transcripts were analyzed thematically (40). An initial coding list was developed based on the topic list, familiarization with the data, and discussion in the research team (NG, KRJ, ALB). Subsequently, NG coded a sample of the transcripts.

9 We will report on the findings related to the procedural ethical aspects of GDT, i.e. the questions, concerns, and implications that relate to the process of governance of and decision-making about GDT, in a separate manuscript.

KRJ critically (re)read this sample of coded transcripts, and the interpretations and suitability of the codes were discussed and compared amongst the research team. The coding list was evaluated and adapted, and all interviews were coded by NG using Nvivo 12 software. The meaning of individual text fragments was determined by interpreting them in the context of the whole interview with the participant in question (41). In the course of analysis, codes were adapted and additional codes were added to the coding list where necessary. A meaning pattern was identified across the data set, leading to the formulation of interpretative higher order themes. Throughout the process of analysis, the research team went back and forth between the different steps to allow for constant comparison. In the last stage, relevant quotes were selected to illustrate the identified themes.

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Results

Out of the 43 experts that were approached, 33 agreed to participate in the study, 8 were unable to participate and 2 did not respond. A total of 33 semi-structured interviews were conducted between November 2018 and July 2019. The interviews lasted between 49 and 114 minutes, with an average duration of 69 minutes. 13 respondents were employed in the United States, 11 in the United Kingdom, 8 in various European countries (Belgium, France, Spain, Switzerland, and the Netherlands) and 1 in Burkina Faso. Interview respondents worked in different disciplines, including the natural sciences (n = 11), philosophy/ethics (n = 9), non-governmental organizations (NGOs; n = 5), policy-making (i.e. professionals working in an organization that is involved in designing policy or regulations for GDTs or that funds gene drive research; n = 5) and various social sciences (n = 3). Those individuals who were working in the natural sciences and affiliated with an NGO (n = 2) were classified as 'natural scientists'.

Three main themes were identified during the data analysis. The moral views of the respondents were principally influenced by their attitudes towards or convictions about (1) how best to deal with the uncertainty related to GDTs; (2) which alternatives should be weighed and how; and (3) their views on nature and the role humans should have in nature. The tables list representative quotations that were selected to illustrate the identified themes. In the following, we indicate the respondents' disciplines only if it helps to contextualize their opinions in comparison to respondents with different stances.

Theme 1: Dealing with uncertainty

Identifying sources of uncertainty

Many respondents stressed the potential of GDTs, yet at the same time reflected on the epistemic (knowledge-related) uncertainty about whether GDTs will be successful at achieving their intended goals. Similarly, many respondents reflected on the difficulty of accurately predicting the potential negative effects of GDTs.

The respondents identified different, interrelated sources of uncertainty. First, some respondents stressed that the proposed applications of GDTs and particular gene drive designs are based on mathematical modeling and limited proof-of-concept studies and are still being developed in the laboratory (Table 1, Quote 1A). Second and relatedly, some respondents identified knowledge gaps that contributed to epistemic uncertainty. These knowledge gaps related to the efficacy and hazards of GDTs in laboratory and cage experiments, population dynamics and sizes of natural populations in which GDTs may be used, and the roles of these populations in their ecosystems (Table 1, Quote 1B). Third, various respondents (all natural scientists) expressed concerns about the technical hurdles that have been encountered in making stable GDTs (Table 1, Quote 1C), in which the necessary components are expressed at the right time, place and level, without excessive fitness costs or resistance occurring. Similarly, some natural scientists reflected on the difficulty of getting GDTs to work in particular species. Finally, several respondents (all natural scientists) reflected on the complexities involved in translating results from the laboratory to the field; results in the laboratory may differ from results in ecosystems, complicating estimations about the effects of GDTs based on laboratory results (Table 1, Quote 1D).

Dealing with epistemic uncertainty

Respondents had different views about the implications of the knowledge gaps and epistemic uncertainty related to GDTs and how this uncertainty should be dealt with. A few respondents (predominantly working within the social sciences and the NGO sector) argued the epistemic uncertainty related to GDTs provided a reason to support a moratorium on applications of GDTs outside the laboratory (Table 1, Quote 1E) ('risks of intervention' stance). Other respondents (working in various different disciplines) instead argued that such an approach would itself be harmful given the problematic status quo. According to them, the problems that GDTs aim to tackle are themselves attended by significant harms, and this should be factored into the decision on whether to use GDTs ('risks of non-intervention' stance). Rather than categorically refraining from applications of GDTs outside the laboratory, they argued more knowledge needs to be obtained about their (intended and unintended) effects through continued phased research to make an informed decision about whether field trials and more general releases should be allowed (Table 1, Quote 1F). Several respondents of the latter group argued that epistemic uncertainty is inherent to the initial stages of technology development and therefore does not provide an argument against developing and at some point testing these technologies (Quote 1G). One respondent, for instance, stressed that these knowledge gaps and related uncertainty do not provide a reason to put GDTs under intense scrutiny this early in the developmental process (Table 1,

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Quote 1H). One respondent argued a certain level of uncertainty could be justified for GDT applications that could be beneficial for human wellbeing (Table 1, Quote 1I).

Importance of setting realistic expectations

Although respondents thus varied in their assessment of how we should deal with the knowledge gaps and uncertainty related to GDTs, respondents with different views agreed that these knowledge gaps and uncertainties have not received enough attention in public and academic debates on GDTs. Various respondents mentioned that GDTs are regularly overhyped or presented as 'silver bullets'. Respondents mentioned varying reasons why such overhyping is problematic and potentially harmful. On the one hand, several respondents (all natural scientists) who were in favor of developing GDTs mentioned that such overhyping could lead to unrealistic expectations about the technology, which could stifle further development if a first GDT release did not live up to expectations (Table 1, Quote 1I). On the other hand, several respondents with diverging views about GDTs (and from different disciplines) argued the silver bullet narrative created a false dichotomy in the debate about GDTs, in which employment of a perfectly functioning technology or acceptance of the status quo are presented as the only potential choices and outcomes, whereas the potential choices and outcomes are much more complex and uncertain (Table 1, Quote 1J).

In sum, respondents with different views on GDTs agreed there is epistemic uncertainty related to GDTs and identified similar knowledge gaps that ought to be addressed. Similarly, they agreed – albeit for different reasons – that realistic expectations should be set in the academic and public debates on GDTs: experts that participate in these debates should openly address the uncertainties and complexities involved in estimating the effects of GDTs. What they did not agree about was whether epistemic uncertainty provides a reason to refrain from testing GDTs outside the laboratory ('risks of intervention' stance) or rather – given the harms of the status quo – a reason to support phased research ('risks of non-intervention' stance). Respondents working in the natural sciences, philosophy/ethics and policy making somewhat more often held the former stance, whereas respondents working in the social sciences and NGO sector more often held the latter stance.

Table 1. Quotations that illustrate theme 1

	(Sub)theme	Quote
	Dealing with uncertainty	
	Identifying sources of uncertainty	
1A	More experimental evidence must be obtained	R1: *"Various designs (..) work mathematically. But sometimes biology is different than theory. So these models should be tested experimentally in the laboratory the upcoming years."*
1B	Knowledge gaps	R21: *"There's a lot we don't know right now and there's much more study that needs to go, that needs to happen before we start releasing gene drives into the environment".*
1C	Technical hurdles	R26: *"All these proof of principle drives that have been published, they're (..) very gentle to the genome, which means that they're easy to show good principals in the lab, but they're not strong enough to be able to spread robustly once you get them into the wild. And so yes, the issue we're encountering now is – we know how in theory we should build them – to make them spread strongly in the wild. But there's just so many engineering hurdles to get that to work, right."*
1D	Translation from laboratory to field	R6: *"There are so many idealizations in populations genetics models that I would not want to stake a whole lot on them being accurate predictors of what happens when you intervene [in the wild]."*
	Dealing with epistemic uncertainty	
1E	Epistemic uncertainty as a reason to support a moratorium	R29: *"I think in terms of the moratorium scientists are not even at the stage yet of asking the right questions about gene drives, let alone building enough understanding of genes and evolution to release gene drives into the environment."*
1F	Epistemic uncertainty as a reason to support phased research in light of the status quo	R12: *"(..) the status quo situation we find ourselves in is already attended by significant harms. That's certainly the case with malaria. (..) [and so] I think we ought to push back a little against this overly precautious approach. And that's not to say I'm going to absolutely support releasing (..) [a] gene drive organism. But I think in order to make an informed decision about whether we should be doing field trials or more general releases, we really need to know more about what the technology can and can't do."*
1G	Accepting a certain level of epistemic uncertainty	R14: *"There are many, many reasons why it might fail in the field (..) but there's a certain point where we have to say "it's good enough and we can't see any obvious reason why it's going to fail".*
1H	Efforts undertaken to study knowledge gaps should be acknowledged	R31: *"It never ceases to amaze me that these things are still years away from actual release and yet they're in the focus of such an intense scrutiny already, and a lot of the questions raised are questions that we're really trying hard to answer and would not go to the field without answering. But, you know, it is bound to cause confusion with the public that we can't answer them yet. (..) It's going to take a while to answer these questions and, in the meantime, the public is getting hit with this uncertainty, uncertainty, uncertainty, and so it's complicated".*
1I	Justifying a 'leap of faith'	R12: *"The big question is going to be when we have to consider potential harms to ecosystems because that's obviously something that's quite difficult to model in constrained environments. So that's going to be the leap of faith at the moment. (..) we're going to have to again, make a balance to think: what are the kinds of important interests that might justify the leap of faith? (..) My view is that (..) it's going to depend on the degree to which the benefit (..) plays a central role in either human wellbeing or the wellbeing of other features in our environment, including animals".*
	Importance of setting realistic expectations	
1J	Overhyping may block further development at a later point	R14: *"There's a genuine risk that we put too much hope and faith in gene drives and that they don't work very well. (..) people need to have a realistic view of what could happen after a gene drive release. And that we don't have an expectation that the gene drive is released and it's the first one and we, you know, are still trying to understand how it might spread, how population dynamics come into it, and migration of the mosquitoes, and seasonal effects. And it spreads for a short while and then fails because something stops it from spreading farther. (..) if these things happen, I don't think that should be a block to further development".*
1K	Overhyping creates a false dichotomy	R32: *"This silver bullet narrative is damaging. (..) if you propose something as a silver bullet, then you're somehow some sort of [curse word] if you decide not to use it if it could be this cure-all. We don't even know if it is, you know? (..) it promotes this binary discussion of "okay, fine, if you don't use it you want all these people to die (..) and no, that's not it. (..) I don't want children to be dying either, but I also don't want us to make decisions based on something like, someone's crazy vision of something that maybe isn't necessarily true yet. We don't know if it is".*

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Theme 2: Identifying and weighing alternatives

Although almost all respondents morally evaluated GDTs by comparing them to alternatives, respondents identified and used different alternatives in their comparisons, resulting in different conclusions about the permissibility of GDT applications. These alternatives can broadly be grouped in two categories: 'downstream' solutions that comprise conventional strategies to target vector-borne diseases, invasive species and agricultural pests, and 'upstream' solutions to these issues that instead comprise systematic changes to global health care, political and agricultural systems.

'Downstream' solutions: comparing GDTs to conventional strategies

Many respondents (from different disciplines) compared GDTs with conventional strategies used to target vector-borne diseases, invasive species and agricultural pests. For applications to target vector-borne diseases, these alternatives included strategies such as insecticides, impregnated bed nets, swamp draining and antimalarial medication; for applications to target invasive species, these alternatives included the use of pesticides, poisoning and ecosystem interventions such as introducing predators. Many respondents argued GDTs should be developed and/or used for particular applications if they provide benefits in comparison to conventional strategies that are currently being used. For example, numerous respondents contended that alternative conventional strategies have thus far been inadequate and/or harmful for the environment, other species or humans. For them, the harmfulness (Table 2, Quote 2A) and inadequacy (Table 2, Quote 2B) of these conventional strategies underline the need for an alternative strategy to tackle these problems, and GDTs could be such a strategy that could be used next to conventional approaches (Table 2, Quote 2C).

'Upstream' solutions: comparing GDTs to systematic changes

Some respondents (mostly working within the NGO sector and the social sciences) instead compared GDTs with large-scale changes in our global health care, political and agricultural systems. According to these respondents, these underlying systems produce the problems we are trying to tackle in the first place, and if we do not look for the solution of the problem at that level, we are merely controlling the symptoms rather than the underlying problems. One respondent, for instance, argued agricultural pests are present due to the way in which we have designed our agricultural system, and should correspondingly be addressed by changing this system rather than by developing GDTs (Table 2, Quote 2D). Similarly, another respondent contended that, rather than develop GDTs, we should target vector-borne diseases by improving living conditions and health care facilities in the areas where these diseases are endemic (Table 2, Quote 2E). Correspondingly, as GDTs do not get to the root of the problems they aim to solve, these respondents considered GDTs an undesirable intervention.

Exhausting alternatives and feasibility of alternatives

Respondents disagreed with each other about whether the alternatives identified by those with a different view were feasible, and about whether they had been sufficiently explored. On the one hand, some respondents that opposed GDTs and argued in favor of 'upstream' solutions also questioned whether the conventional 'downstream' strategies to deal with vector-borne diseases and invasive species have been exhausted (Table 2, Quote 2F). On the other hand, some respondents who were open to (applications of) GDTs and considered other 'downstream' approaches insufficient or harmful, argued that the systematic 'upstream' changes advocated by opponents of GDTs to solve the problems at hand may be desirable, but not feasible. According to these respondents, past efforts and future projections by organizations such as the World Health Organization (WHO) demonstrate that it is naïve to think that the social determinants of health could be increased to such an extent that malaria transmission could be stopped (Table 2, Quote 2G).

Table 2. Quotations that illustrate theme 2

	(Sub)theme	Quote
	Identifying and weighing alternatives	
	Comparing GDTs to conventional strategies	
2A	Conventional strategies are harmful, underlining the need for an alternative strategy	R18: *"Our current [anti-malarial] tools, they do have a negative effect. We treat it as being the status quo and so therefore we don't measure the negative effects, but every pesticide we use on an environment still has a negative, [whichever] we choose. You should compare like with like, but it's very infrequent that people compare like to like, we have a much greater fear of the new and the novel, as opposed to the cost that we are having already (..) Let's not say our [anti-malarial] tools are currently not teratogenic or highly problematic to human health".*
2B	Conventional strategies are inadequate, underlining the need for an alternative strategy	R5: *"The tools we have are good because they've saved lives but they're not perfect or sufficient. Which is why we need something new and this could be it."*
2C	GDTs are complimentary to conventional strategies	R14: *"It doesn't take anything away from what we are already doing. (..) it adds to all of the different interventions. (..) Even if they were around the corner, even if they got used and even if they were being successfully used, don't stop the other interventions. You'd be mad to do that."*
	Comparing GDTs to systematic changes to global health, political and agricultural systems	
2D	Agricultural change is needed to solve the problem of agricultural pests	R11: *"Like if you want to use [gene drives] in agriculture, what does that mean? Are we going to eliminate pests, so called pests, that actually are there because of the way we have chosen to do agriculture, which has proven to be a real problem for the climate, as well as for biodiversity?"*
2E	Health care and political change is needed to target vector-borne disease	R16: *"I would say at many places it's mainly a political thing. If you have like [a] good water system, good hospitals, good access to treatment; that would make that the malaria issue is much less problematic"*
	Exhausting alternatives and feasibility of alternatives	
2F	Questioning whether conventional strategies have been exhausted	R29: *"You can look at countries like Paraguay and a number of other countries that have recently been declared as malaria-free, and there's a lot of really wonderful studies as to what they did. I mean, there are so many approaches from the policy level to the grassroots level and education; so many different strategies and tactics that all need to be implemented."*
2G	Changes in global health care, political and agricultural systems not feasible	R18: *"You would need to spend a crazy amount of money in the sites where we work to be able to reach the social determinants of health high enough to stop malaria transmission, it would be huge, it's unattainable"*
2H	Difficulty in deciding what should be taken as a given or as changeable	R6: *"This is the very hard thing in this area, is to say what to keep fixed".*

All in all, most respondents morally evaluated GDTs by comparing them to alternatives, yet respondents held very different views on which alternatives should be considered (un)feasible and (in)sufficiently explored, and likewise which aspects of the global health care, political and agricultural systems should reasonably be taken as a given or as changeable. These different views, which may be summarized as 'downstream solutions' and 'upstream solutions' stances, were based on both empirical convictions about past efforts and future projections, as well as on normative convictions about the permissibility of using technology to solve problems that are (in part) caused or exacerbated by social or political processes. Respondents working within the natural sciences, philosophy/ethics and policy making were somewhat more inclined to have a 'downstream solutions' stance, whereas respondents working in the social sciences more often referred to the importance of 'upstream solutions'. These different stances underline a core feature of disagreement about the moral permissibility of using GDTs.

Theme 3: The role of humans in nature

Finally, respondents had diverging views on what they considered justifiable interventions in nature, and whether GDTs could be considered a justifiable intervention. In other words, respondents differed in their assessment of what the role of humans in nature should be, and whether it is morally permissible to intervene in wild ecosystems in this way.

Assessing the moral permissibility of interventions in nature

Several respondents (none of whom were scientists or policy makers) argued we should not intervene in nature by using GDTs ('non-interference' stance). According to these respondents, the natural state of affairs is something that ought to be protected, and that would be disrupted by the use of GDTs. By using GDTs, some of them argued, humans would take up the role of 'designers' of nature, and this would be morally impermissible (Table 3, Quote 3A). Several respondents stressed these concerns about the role that humans should have in nature do not just apply to the use of GDTs, but are rather a part of broader concerns about the negative impact of humans on earth. These respondents emphasized that the human relationship to nature is largely skewed towards changing nature, rather than living in balance with nature and trying to preserve the natural state of affairs, and that this is generally undesirable (Table 3, Quote 3B). A few respondents mentioned it could be considered specifically problematic if suppression drives were used to eradicate unwanted populations or species (Table 3, Quote 3C).

Other respondents (from different disciplines) disagreed with this view on the role of humans in nature and did not have fundamental problems with interfering in nature ('interference' stance). Some of these respondents argued that we intervene in nature all the time, and generally appear to consider it morally permissible to do so. Rather than looking specifically at GDTs, some of these respondents argued we should look comparatively at other interventions in nature that we consider morally permissible. If we consider other drastic interventions in nature morally permissible, it would be inconsistent to object to GDTs on the grounds that these technologies would be used to intentionally change nature (Table 3, Quote 3D). Some of these respondents also criticized opponents' views on another ground, namely that they have an overly optimistic view of the goodness of nature. According to these respondents, nature is characterized by suffering and pain (as is, for instance, illustrated by the suffering of many wild animals). In their view this suffering provides moral grounds to intervene in nature, rather than to preserve it as it is (Table 3, Quote 3E). Other respondents questioned whether something like a 'natural' state of affairs that can be preserved actually exists. These respondents contended we should not see the current distribution of organisms as the 'natural' state of affairs which ought to be protected from human influence, as nature has been influenced by humans for millennia (Table 3, Quote 3F). According to these respondents, these in their opinion incorrect views of nature (as either inherently good or untouched and pristine) lead to unjustified conclusions about the impermissibility of using GDTs in nature.

Balancing the value and interests of humans, non-human animals and the environment

The positions of respondents about the role humans should take in nature were also related to their opinions about the value and interests of humans, non-human organisms and the environment, and how these should be balanced in decision-making about whether (and if so, under what conditions) to use GDTs. Various respondents argued that human interests outweigh the interests of non-human animals and the environment (Table 3, Quote 3G). Other respondents questioned the way in which human interests always take precedence over the value and interests of non-human animals and entities, and argued the latter are insufficiently taken into account (Table 3, Quote 3H). Several other respondents argued that the interests of humans should not trump the interests of non-human animals and the environment, and that GDTs should thus not be used (Table 3, Quote 3I). Others instead argued that these considerations limited potentially justifiable applications of GDTs to those applications that would achieve great benefits for humans (such as public-health benefits) while minimally affecting non-human animals (Table 3, Quote 3J).

Table 3. Quotations that illustrate theme 3

	(Sub)theme	Quote
	The role of humans in nature	
	Assessing the moral permissibility of interventions in nature	
3A	We should not take up the role of designers of nature by using GDTs	R30: *"[I] have a problem with it, there is this nagging idea, that (..) we have this ability to say in a finite way "we're changing this organism and we're going to turn this organism from a vector into some type of benevolent tool for our use."*
3B	Concerns about the role of humans in nature are part of broader concerns about the impact of humans on earth	R24: "[*There is this] very fuzzy sense that it's nice to try to preserve the natural state of affairs. (..) [We should preserve] the human relationship to nature and the desire to live with the world rather than always changing the world. (..) We're doing an incredibly bad job of that. There's no balance whatsoever at the moment, and gene drives are, you know, not the main story. The main story is (...) climate change, and total ecosystem disruption, deforestation and pollution. (..) But in so far as you know, we're talking about the ethics of gene drives (..) I do think about (..) applications in that way."*
3C	It would be impermissible to suppress or extinct species that humans consider undesirable	R24: *"There's a sense in which gene drives can be thought of as extinction technologies. They're getting rid of something you don't want, either the whole population or a subpopulation, the whole species potentially. Or if it's just a genotype, a phenotype, that you don't want, you're trying to get rid of that and turn it into something else. Get rid of the gregarious desert locust, and force it to be this other thing that you think will work better with human life. And those applications that really sort of live into that extinction ideal – if it's a native organism, like the desert locust, you're fiddling with it in its home range – are intrinsically somewhat less attractive to me."*
3D	We should compare interventions with GDTs to other interventions in nature that we consider morally permissible	R6: *"I suppose one context in which we'd want to put is to look comparatively at the kind of interventions we're very happy to do in nature without any without much notion what the consequences will be. And for you know with perhaps much lesser potential benefits, I mean clear cutting a large forest or something (..), probably changing the environmental, meteorological, all kinds of factors in unpredictable ways. Probably for very questionable goals like replacing them with a large plantation of food stuff. (..) it has some relevance to evaluating the way we should think about this kind of intervention, and we should remember that we intervene all the time."*
3E	Nature is not good, and this provides a reason to intervene	R22: *"[There are] people who feel that nature is important on a spiritual level and that it [should be] unaffected by humanity as much as possible. (..) I completely disagree because in my view much of nature is – well, nature is amoral and that's a bit of a problem because when you look at it with a moral lens you see an awful lot of animals suffering. (..) I'm not at all convinced that nature is good."*
3F	GDTs do not intervene in a 'natural' state of affairs	R5: *"A lot of the ethical debate around gene drive has the preconception or the assumption that nature is still in a natural state (..) they fail to recognize that there is a[n] (..) assumption from the beginning: that nature created by whatever force is perfect. And then it's perfect and what we're doing today [in] 2019 is affecting it. But we've been here for a really long time."*
	Balancing the value and interests of humans, non-human animals and nature	
3G	Human interests outweigh animal and environmental interest	R26: *"I'm big on (..) trying to check my privilege (..). [if] you're a westerner, ecology is allowed to be your biggest concern, versus someone who lives in Africa whose children are dying. And as a human, like, our biggest concerns are human concerns."*
3H	The way in which human interests always take precedence should be questioned	R30: *"I think we have a very contentious, a very bizarre relationship with nature. (..) [I] think it can be universally agreed upon [that] nature, however you define it, is shrinking and it's shrinking because we're ever-expanding. And so the question is: As we ever-expand, what does that mean for us and what does that mean for whoever lives in the remaining nature that still exists? Do we have any obligation being the critter who's the most exploitative of the planet, the most inconsiderate, the most free-ranging here, and the most volatile and the most detrimental to other species, how do we and do we have an obligation? Is there any kind of moral obligation to take that into account?"*
3I	The interests of humans should not trump the interests of non-human animals and the environment	R19: *"I'm seeing, more and more, human beings as part of the whole biosphere and therefore not just having a special claim in a way. Of course I'm a human, so in that sense I can see why, but it seems to me as though humans have been making a special case for their own interests for a very long time, and I don't know where that's got us (..) Between the application of (..) island invasive species and malaria, on the surface of it there might seem to be an ethical difference, but in the greater picture of a planet and the fact that we have to change our attitudes to this planet (..), I don't."*
3J	Taking the value and interests of the non-human into account provides conditions for use of GDTs	R32: *"It becomes particularly complicated when we're faced with something like a public-health imperative. (..) How can you say mosquitos are important enough not to save 500,000 lives a year? (..) There must be ways we can uphold both and something like compassion (..) [for both] people who are dying (..) [and] for the environment that could be damaged by making these choices. (..) For example, if you feel the flourishing of both should be supported, then a strategy that has the potential to drive the species to extinction probably doesn't fit in that model (..). It doesn't mean there might not be other strategies that could still succeed in reducing malaria transmission through genetic modification of mosquitos."*

In summary, respondents held different views on what the role of humans in nature should be, whether or not there is a moral reason to preserve the 'natural' state of affairs, and how the value and interests of humans, non-human animals and the environment should be balanced. Views on these issues influenced their views on GDTs and contributed to different stances on whether applications of GDTs could be justified, and if so, under what conditions. On these grounds, some respondents considered it permissible to intervene in nature using GDTs ('interference stance'), whereas others did not ('non-interference stance'). Natural scientists and policy makers were more inclined to hold the former stance, whereas respondents working within philosophy/ethics, the social sciences or NGOs were somewhat more inclined towards the latter.

Discussion

As far as we know, this study is the first in-depth interview study in which the moral views of a broad range of GDT experts were investigated. Our analysis sheds light on the considerations that influence the moral views of experts about the permissibility of (applications of) GDTs. Three main themes were identified: (1) how the uncertainty related to GDTs should be approached; (2) the alternatives to which GDTs should be compared and how these alternatives should be weighed; and (3) the role humans should have in nature.

In what follows, we will reflect on the implications and relevance of our empirical study for the debate on GDTs, relate its findings to the broader literature, and identify areas for further research. First, we will reflect on those issues about which experts largely agreed. Subsequently, we will discuss the disagreements that the study identified and underline issues that demand further (normative) reflection. Finally, we will outline some limitations of our study and provide recommendations for future research.

Common ground

To start, this analysis points to issues about which experts with different moral views on GDTs were in accordance, even if their overall views on the moral permissibility of these technologies differed vastly. First, experts with different moral views identified similar concerns with regard to the existing knowledge gaps for particular gene drive designs and applications, technical hurdles that would need to be overcome, and areas of uncertainty related to translation of results obtained in the laboratory to effects in the wild. Those with fundamentally different views on GDTs thus nonetheless agree that knowledge gaps exist and that more knowledge about particular topics should be obtained.

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Second, experts pointed out that it is important to set realistic expectations about the complexities and uncertainties involved in estimating the effects of GDTs, both in terms of the potential benefits and risks. The importance of openness and transparency about uncertainties about both potential benefits and harms have been recognized by various organizations and authors in the GDT field (e.g. (42–44)), yet the results of our study emphasize that GDT experts nonetheless continue to see overhyping of these technologies as a risk. This is a relevant finding since expectations about new and emerging technologies are 'performative': they do not merely constitute representations of potential future scenarios, but also contribute to shaping the future, for example by influencing agenda setting and resource mobilization (34,45–47). As discussions on hype underline, expectations about emerging technologies can also have concrete undesirable impacts. For GDTs, it has been noted that unrealistic expectations could lead to premature calls for their release (1). Furthermore, hyping could distort publics' and communities' understanding and expectations of these technologies, and potentially lead to a loss of credibility or trust if expectations are not fulfilled (45,47). Additionally, unrealistic expectations may divert resources away from alternative strategies that may in fact be better suited to tackle a particular problem. This may be seen as especially problematic in view of concerns about path dependency, the idea that investment in one particular solution to a problem makes it harder to switch to another solution even if it turned out to be superior (12,45).

For GDT experts, and in particular GDT scientists, it is thus important to balance enthusiasm - which is both understandable and necessary to build momentum and raise funds in any scientific endeavor (48) - with the concomitant responsibility to be open about complexities, uncertainties and knowledge gaps. Moreover, this confirms the importance of obtaining more information to address current knowledge gaps, realistically weighing different alternatives to achieve particular aims (9) and designing adequate evaluation and mitigation plans (1). Furthermore, it could be valuable to make different visions about GDTs themselves a subject of analysis throughout the process of their development. As the literature on 'sociotechnical imaginaries' illustrates, these visions are strongly influenced by broader visions of desirable futures (49). A critical analysis of these different visions enables a transparent discussion about the plausibility and desirability of the different underlying arguments, premises and imaginations in which they are grounded, and could thereby help provide orientation on GDTs (34,50).

Sources of disagreement

For each of the three themes that were identified, there were also fundamental disagreements; whilst experts with different opinions agree on particular (empirical) issues, they disagree about what we should do in light of these issues. In what follows, the sources of these disagreements will be explored in more detail.

Disciplinary differences

In previous studies, it has been posited that professionals from different disciplines have different approaches that affect their views on emerging technologies. For example, Ndoh, Cummings and Kuzma (51) describe disciplinary culture as a factor in risk perception. In their study, natural scientists for instance had lower expectations of human and environmental hazards of a synthetic biology case study than social scientists. Amongst other things, these differences may be explained by disciplines' different epistemological underpinnings and knowledge approaches, which each have their own preoccupations, strengths and weaknesses (52). These different disciplinary approaches are also tied to different value-based positions (53).

In our study, respondents working in the natural sciences, philosophy/ethics and policy making were somewhat more inclined to have 'liberal' stances (that leaned towards deploying GDTs) in relation to the three themes that were identified, whereas respondents working in the social sciences and NGO sector were more inclined to have 'conservative' stances (that leaned towards refraining from deployment of GDTs outside the laboratory). Whilst our study was set up with the aim of studying the moral views of a wide range of GDT experts rather than studying the influence of disciplinary cultures on these views, these differences underline the relevance of interdisciplinary collaboration in the development of and decision-making about GDTs, for each discipline can contribute its own insights and perspectives. At the same time, there was also significant variation in stances *within* groups of respondents working in the same discipline, demonstrating that the differences in moral views could not be attributed or reduced to the respondents' disciplinary cultures. In the following sections, we will therefore get to the heart of these disagreements by investigating the basis for the identified tensions in more detail.

Consequences of knowledge gaps and epistemic uncertainty

The first source of disagreement that was identified concerns the consequences of the knowledge gaps and epistemic uncertainty related to GDTs. Epistemic uncertainty is widely recognized as a persistent characteristic of new and emerging technologies in general and of GDTs in particular (1,3,10,21,44). As has also been recognized, reducing epistemic uncertainty about the risks of GDTs could paradoxically require an environmental release that itself poses risks[10] (21,25), underlining the importance of determining when knowledge gaps can be considered sufficiently resolved to make responsible decisions about specific GDT applications (25,54).

In our study, some respondents argued the knowledge gaps and uncertainty provide a rationale to proceed with phased testing (potentially including, at some

10 As has been recognized by GDT experts in a workshop on gene drive governance and research needs, the use of localized rather than self-sustained GDTs could reduce this complexity (25).

point, field testing) to obtain more data, whereas others argued there should be a moratorium on any application of GDTs outside the laboratory. Whilst both groups of respondents argued that it is important to prevent risks and harms, they operationalized this differently: the latter group contended greater precaution should be taken against the risks and harms associated with the *use* of GDTs ('risks of intervention' stance), whereas the former group instead placed greater weight on the opportunity costs associated with *failing to use* GDTs ('risks of non-intervention' stance) and argued proceeding with GDT deployment could be acceptable even if uncertainty remained.

3

The identified stances can also be recognized in broader disputes between those that respectively take a 'precautionary' or a 'proactionary' stance toward emerging technologies, in which the latter have argued that precaution in one respect often leads to increased risks and harms on other fronts (55–57). A crucial point of difference between these different parties also relates to who should bear the burden of proof with regards to a technology's potential to cause harm, with those that consider novel technologies 'guilty until proven innocent' versus 'innocent until proven guilty' at opposite sides of the spectrum (56). At the same time, it has also been argued that it could be possible to escape this polarization by distributing the burden of proof (56), explicitly framing precautionary courses of action as precautionary "*with respect to* something" (p. 469) (55), and looking for a middle ground of 'optimal' rather than 'maximum precaution' (58). Whilst these proposals may not resolve the dispute between those with different stances, they may nonetheless help to bring points of disagreement more squarely into focus in related discussions. Moreover, these different stances invoke discussion about other related questions such as what constitutes a 'benefit' or a 'risk' in the first place (44,59), and how potential benefits and risks should be weighed.

Weighing of alternative strategies

The second source of disagreement that was identified in this study concerns the weighing of alternative strategies to confront vector-borne diseases, invasive species and agricultural pests. Whereas many respondents compared GDTs to other 'downstream' solutions such as pesticides, other respondents argued 'upstream' solutions that tackle these problems at their root should be deployed instead. Some respondents, for instance, stressed that the impact of vector-borne diseases such as malaria is also determined by social and political factors, and argued that deploying GDTs would thus not offer lasting solutions. These different stances were also mentioned in the report of a workshop that identified governance issues and research needs in relation to GDTs (25).

To some degree, these different stances may be attributable to a different understanding of the empirical data on the efficacy of past efforts to confront these problems and the factors that influence future projections of success if these strategies

are continued or intensified (12). To the extent this is the case, making empirical convictions about both 'downstream' and 'upstream' alternatives to GDTs will further (policy) discussions about GDT. However, these different stances also point to deeper normative questions about the (im)permissibility of 'technological fixes', a recurrent theme in debates about biotechnology (60) that has also received some attention in the debate on GDTs (12,44,61). Such techno-fixes have, amongst others, been critiqued on the ground that they reduce a social problem to a technical problem, which could both perpetuate the underlying problem (1,61) and result in problematic side-effects (44). Moreover, it has been argued that techno-fixes are based on mistaken convictions about the inherent progressiveness of science and technologies (60). At the same time, it has been noted that the comparatively quick and targeted nature of GDTs could nonetheless make them an attractive solution (1), raising relevant questions about whether we ought to take 'ideal theory' or 'non-ideal theory' (which focuses on what we ought to do in non-ideal circumstances) as a starting point for ethical decision making about GDT.

3

Intervening in nature

A third normative dispute related to the permissibility of using GDTs to intervene in nature for our aims and benefit. Experts' views of nature and the role of humans in it, as well as their views on the value and interests of humans, non-human animals and the environment, impacted their moral view on intervening in nature with (particular applications of) GDT. Views of nature and what is 'natural' have been found to influence views on a broad range of emerging technologies (62,63) and have long since led to debate about the ideal of nature and the (ir)relevance of naturalness as an ethical criterion (9,64,65). As has also been pointed out, people across the world moreover tend to have different views of (the role of humans) nature (44), underlining that it would be highly relevant to study how related perspectives affect non-Western experts' and publics' moral views of GDT.

In the literature about GDT, various authors and organizations have indeed pointed out that perspectives on the relationship of humans to nature play an important role in the debate about these technologies (1,29,31,44,66). Relevant points of contention in this debate include if and on what grounds human independence is valuable in (wild) species and ecosystems (44,61), if and on what grounds GDTs differ in morally relevant ways from other interactions with non-human nature (44,66) and if and on what grounds it is permissible to genetically modify non-human organisms to achieve conservation goals rather than changing human behavior to achieve these goals[11] (61). As the results of our study imply, stances about the permissibility of intervening

11 In this sense, the third theme is interrelated with the discussion on techno-fixes, which calls the permissibility of doing so into question. Indeed, techno-fixes have also been critiqued on the ground that they derive from a commitment to an anthropocentric conception of the human relationship to the (rest of) nature (60).

in nature in this way also hinge on convictions about the value or moral status of different organisms, what duties we have towards these different entities, and how duties towards different entities should be prioritized in case they conflict. Although these featured less prominently in respondents' statements, convictions about the value or moral status of holistic entities such as species (13) and ecosystems are likely to be of similar relevance.

For all these different normative disputes, critical analysis and explicit discussion can help to disentangle the complexity of the problems at hand, challenge potentially unwarranted assumptions and enable individuals to develop well-considered judgements on these issues. GDT experts, which actively shape these technologies and the debate about them, may take the stances and considerations outlined in this paper as a starting point for further reflection on their (implicit) views on these matters and how these affect their views on GDT. At the same time, it is important to realize that genuine value pluralism about many of these issues will remain (67), underlining the need for fair governance and decision-making procedures. Amongst others, important procedural ethical questions relate to who should make decisions, how these decisions should be taken, and when deliberation should be concluded (1,15–17).

Limitations and recommendations for future research

Our results should be interpreted in the context of the following limitations. First, the scope of our study was relatively broad. As it was the first large and in-depth interview study on experts' moral views regarding GDT, we chose to conduct an exploratory study to allow experts to bring up issues they considered relevant. Although saturation was reached on the codes and themes identified, further research should explore these topics in more depth. Second, any qualitative interview study is prone to interviewer and researcher bias; a different interviewer could have focused their attention on different aspects of the respondents' answers, and grouped the codes and themes differently. Third, our study represents a subgroup of GDT experts which prominently contributed to the academic and/or policy debates on GDT. While these experts offered a diverse range of perspectives, they were predominantly employed in the global North. It would be highly relevant to conduct additional qualitative interview studies with experts in other countries to investigate whether there are cultural or otherwise region-dependent differences amongst experts. In particular, it would be relevant to focus on respondents from countries where GDTs may be used to combat vector-borne diseases and/or invasive species, such as Burkina Faso, Ghana, India, Australia and/or New Zealand. Similarly, it would be very relevant to conduct a qualitative study amongst the communities living in areas where GDTs may be deployed. Finally, many of the issues identified in this study warrant a more detailed normative analysis.

Conclusion

GDTs are developing rapidly and have been proposed as a potential strategy to address several major problems, but have also raised a range of ethical questions. These technologies themselves, the academic debate on the associated ethical questions, and the related policymaking are shaped by experts from different disciplines. This interview study helps to disentangle the polarized debate on GDTs by providing a better understanding of the moral views of GDT experts and elucidating where they agree and disagree. The obtained insights provide valuable stepping-stones for a constructive debate about underlying value conflicts and point to topics that deserve further academic scrutiny. Further evaluation of these and other morally relevant aspects of GDTs should take place in co-production with diverse stakeholders in parallel to the technological development of GDT. In this way, these considerations can inform the design and implementation of these technologies and facilitate their responsible development.

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Appendix

As specified in the Methods 'Data collection' subsections of Chapters 3 and 4, the interviews consisted of open-ended questions related to the potential benefits, risks, broader ethical implications, and governance of gene drive technologies. The semi-structured design of the study ensured consistency in a number of topics to be discussed by all participants, while also allowing participants to bring up or emphasize particular new issues they considered relevant.

1. Can you introduce yourself and explain in what way you are involved with or have experience with gene drive technologies?
2. How do you view gene drive technologies based on your experience?
    a. Potential benefits, risks, hazards, ethical implications?
    b. How should we deal with these?
3. How do you view the different potential applications of gene drive technologies (eradicating vector diseases, controlling invasive species, controlling agricultural pests)?
4. How do gene drive technologies relate to alternative strategies to achieve these goals, in your opinion?
5. Various types of gene drives, as well as various gene drive designs are under development. Do you know these different gene drives, and if so, how do you view these?
6. What are, in your opinion, conditions under which gene drive technologies could be used, or limits that should be in place?
7. Who should make decisions about the development and possible use of gene drive technologies? What should, for example, be the role of scientists, the government or governments, and citizens?
8. Do you have experience with current regulation or safety standards for research with (and development of) gene drive technologies? If so, what do you think of the current regulation and safety standards/what should be addressed in such regulations or standards?
    a. Should this be approached in an international context? If so, how?
9. How should gene drive research develop, as far as you are concerned?
    a. For example, what would be needed to draw conclusions about whether or not gene drive technologies should be applied and if so, how?
10. Are there topics that have not been addressed that you would still like to discuss?

3

4

GOVERNING GENE DRIVE TECHNOLOGIES: A QUALITATIVE INTERVIEW STUDY

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Abstract

Background
Gene drive technologies (GDTs) bias the inheritance of a genetic element within a population of non-human organisms, promoting its progressive spread across this population. If successful, GDTs may be used to counter intractable problems such as vector-borne diseases. A key issue in the debate on GDTs relates to what governance is appropriate for these technologies. While governance mechanisms for GDTs are to a significant extent proposed and shaped by professional experts, the perspectives of these experts have not been explored in depth.

Methods
A total of 33 GDT experts from different professional disciplines were interviewed to identify, better understand, and juxtapose their perspectives on GDT governance. The pseudonymized transcripts were analyzed thematically.

Results
Three main themes were identified: (1) engagement of communities, stakeholders, and publics; (2) power dynamics, and (3) decision-making. There was broad consensus amongst respondents that it is important to engage communities, stakeholders, and publics. Nonetheless, respondents had diverging views on the reasons for doing so and the timing and design of engagement. Respondents also outlined complexities and challenges related to engagement. Moreover, they brought up the power dynamics that are present in GDT research. Respondents stressed the importance of preventing the recurrence of historical injustices and reflected on dilemmas regarding whether and to what extent (foreign) researchers can legitimately make demands regarding local governance. Finally, respondents had diverging views on whether decisions about GDTs should be made in the same way as decisions about other environmental interventions, and on the decision-making model that should be used to decide about GDT deployment.

Conclusions
The insights obtained in this interview study give rise to recommendations for the design and evaluation of GDT governance. Moreover, these insights point to unresolved normative questions that need to be addressed to move from general commitments to concrete obligations.

Introduction

Gene drive technologies (GDTs) bias the inheritance of a particular genetic element within a population of non-human organisms, thereby promoting its progressive spread across this population. If successfully developed and deployed, GDTs may be used to counter intractable problems. GDTs could, for example, be used to target vector-borne diseases such as malaria and to control invasive species and agricultural pests that humans thus far have been unable to resolve through other means such as bed nets, insecticides and pesticides (1–3). Various types of GDTs using different molecular mechanisms have been proposed, ranging from non-localized gene drives intended to spread throughout a population or species, to localized or threshold-dependent gene drives that are spatially or temporally limited in their spread (4,5). In the past few years, GDTs have advanced substantially, raising the prospect of moving from laboratory experiments to environmental field studies with gene drive organisms[12] (6).

The possibility of using GDTs to alter organisms in our shared environment raises a range of ethical questions and issues. One key issue in the debate on GDTs is how their development and potential deployment can be guided responsibly – in other words, what governance[13] is appropriate for these technologies. As has been recognized in the literature, GDTs have a large transformative potential: they could have significant benefits as well as harms and could affect a wide range of stakeholders (7–9). This raises moral questions about how the various interests should be balanced, who should be involved in decisions about the development and deployment of GDTs, and in what way. In discussions about these matters, there has been particular attention to the role that communities living near the site of field trials should play (10,11). It has also been noted that GDTs could spread across national borders, such that their governance warrants a transnational approach (4,12). Additionally, the development of GDTs is likely to encompass long-term transnational collaboration between researchers in high-income countries (HIC) and low- and middle-income countries (LMIC), where GDTs are most likely to be deployed given the higher incidence of vector-borne diseases (4).

Emerging technologies such as GDTs have several features that make procedural validity and fairness especially important for the legitimacy of governance procedures (8,13–15). First, GDTs are characterized by substantial uncertainty about the potential benefits and risks of their deployment due to the inherent complexity of ecosystems and the limitations of the extent to which laboratory conditions and mathematical models can model the real-world (8,9,16,17). In addition, different stakeholders have

12 Organisms whose genomes have been genetically altered with a gene drive to spread a desired gene alteration through a population. GDTs could only be used in organisms that have an inheritance pattern that can be biased, which typically means that they reproduce sexually (5).
13 Technology governance may be defined as the "process of exercising political, economic and administrative authority in the development, diffusion and operation of technology in societies" (57). Governance thus encompasses a broad range of mechanisms to steer technology development, including but not limited to regulation (9,57).

ambiguous understandings of the prospects that GDTs offer and divergent moral views on whether, and if so under what conditions, to deploy GDTs (16). Ambiguity makes it difficult to come to a shared understanding of the substantive criteria that governance decisions should be based on, and uncertainty complicates the evaluation of such criteria (8,17). For these reasons, procedural criteria are all the more important (8,10,13–15).

Different policies have been proposed to govern GDTs, ranging from voluntary consensus statements to (inter)national regulation. Various policy papers and consensus statements have been published in which academics and scientific organizations have outlined recommendations and principles for GDT research and policymaking (4,18–26), ranging from safety recommendations for laboratory research (19,21) to core commitments for field trials with localized GDTs (25). These manuscripts provide recommendations for different actors that play a role in GDT research and development, including researchers, policy makers and funders of GDT research. Moreover, academic associations and scientific authorities have published guidelines on GDTs and related policy-making (4,27–31). Finally, GDTs are governed by various national and transnational agreements, such as the National Environmental Policy Act (NEPA), the Convention on Biological Diversity (CBD) and its Cartagena Protocol on Biosafety (6,32).

While governance mechanisms for GDTs are to a significant extent proposed and shaped by professional experts in the field, the published consensus papers and policy papers are by their nature inapt to explore the convictions of these experts and potential differences between them in more depth. It is valuable to study the perspectives of GDT experts as doing so can deepen the understanding of governance issues by providing insights into how they view and weigh different ethical aspects (33). Moreover, it can help to identify questions and concerns that have thus far been underrepresented in the literature, and thereby broaden the scope of issues that warrant further evaluation. In this study, we therefore investigated experts' perspectives on GDT governance through a qualitative interview study. We considered it important to investigate the perspectives of GDT experts as they are likely to shape both the design of GDTs and to influence related governance frameworks[14].

14 At the same time, it should be noted that the expertise relevant to GDT governance is not limited to professional expertise on GDTs, but importantly also includes what has been called the 'experiential expertise' (58) of community members living near potential GDT trial sites. Indeed, professional experts on GDTs may be laypersons on other topics of relevance to GDT governance (59), such as expertise of the local environment and social-cultural context and having personal knowledge of the illness or problem that the release of GDT organisms would address (60,61).

Methods

The findings reported here are part of larger qualitative interview study that investigated professional experts' moral views on GDTs. Qualitative interviews are a valuable method to identify, better understand, and juxtapose people's perspectives; in this way, qualitative research can improve the understanding of ethical implications of a technology by providing insights into how interviewees contemplate different ethical aspects (33). This article reports on the findings related to the procedural ethical aspects of GDTs, i.e. the questions, concerns, and implications that relate to the process of governance of and decision-making about GDTs[15]. In what follows, we provide a concise summary of the study methodology, which has been described in more detail elsewhere (16).

Participant selection and recruitment

Participants were considered eligible for study inclusion if they had contributed to academic publications and/or policy documents on GDT research and development. Eligible participants were identified through a review of the academic (34) and policy publications on GDTs and based on recommendations by previous participants, i.e. through snowball-sampling. The research protocol was submitted to the research ethics committee of the University Medical Center Utrecht for review before initiation of research. The committee determined that this study was exempt from the Medical Research Involving Humans Act (research proposal no. 18/618). In line with the submitted research protocol, participants were first informed about the study and agreed to participate via e-mail, and verbal informed consent for participation in the interview, recording of the interview and data analysis of pseudonymized transcripts was obtained prior to the start of the interview. Recruitment was ended when saturation was reached, i.e. when subsequent interviews no longer brought up new issues ('coding saturation') and the formulated themes were sufficiently understood ('meaning saturation') (35).

Data collection

Semi-structured interviews were conducted by NG. The interview guide for the interviews (see Chapter 3, Appendix) was based on a previous review of the ethical arguments related to GDTs (34) and discussions amongst the research team. The interviews consisted of open-ended questions related to the potential benefits, risks, broader ethical implications, and governance of GDTs. This semi-structured design allowed participants to bring up or emphasize specific issues they considered relevant,

15 The findings related to the substantive ethical questions, concerns, and implications of GDTs – i.e. those questions, concerns, and implications that relate to "what is right in terms of duties, rights, and values (..) independent of any decision-making procedure" (62) (p. 155) have been reported elsewhere (16). A detailed description of the methodology of the study, in line with the consolidated criteria for reporting qualitative studies (COREQ), has also been provided in that publication.

whilst also ensuring some consistency in the topics that were discussed to explore how different participants viewed these topics. The interviews were recorded, transcribed verbatim, and pseudonymized.

Data analysis

The pseudonymized transcripts were analyzed thematically (36). An initial coding list was developed based on the topic list, familiarization with the data, and discussion in the research team. Subsequently, NG coded a sample of the transcripts. KRJ critically (re)read this sample of coded transcripts, and the interpretations and suitability of the codes were discussed and compared amongst the research team. The coding list was evaluated and adapted, and all interviews were coded by NG using NVivo 12 software. A research assistant, IP (see acknowledgements), also coded 20 interviews, and the coding between NG and IP was compared. The meaning of individual text fragments was determined by interpreting them in the context of the whole interview with the participant (37). In the course of analysis, codes were adapted, and additional codes were added to the coding list where necessary. A meaning pattern was identified across the data set, leading to the formulation of interpretative higher order themes. Throughout the analysis process, the research team went back and forth between the different steps to allow for constant comparison. Finally, relevant quotes were selected to illustrate the identified themes.

Results

Out of the 43 experts that were approached, 33 agreed to participate in the study, 8 were unable to participate and 2 did not respond. A total of 33 semi-structured interviews were conducted between November 2018 and July 2019 with experts from different disciplines and countries (see Table 1 for respondent characteristics). The interviews lasted between 49 and 114 minutes, with an average duration of 69 minutes.

Table 1. Respondent characteristics

Discipline	*n*
Natural sciences*	11
Ethics/philosophy	8
Non-governmental organization (NGO)	5
Policymaking	4
Social sciences	4
Country of primary employment	
United States	13
United Kingdom	11
Other European countries (BE, FR, SP, CH, NL)	8
Burkina Faso	1

* Respondents who worked in the natural sciences and were affiliated with an NGO (n = 2) were classified under 'natural sciences'.

The respondents brought forward a range of issues they considered of importance for the governance of GDTs. Broadly, these could be clustered around three main themes: (1) engagement of communities, stakeholders, and publics; (2) power dynamics, and (3) decision-making. In what follows, we discuss the different issues that were raised by the respondents in relation to these themes. The tables list representative quotes that were selected to illustrate the identified themes.

Theme 1: Engagement of communities, stakeholders, and publics

Almost all respondents agreed that it is important to engage communities, stakeholders, and publics[16] in GDT research, yet they had diverging views on the motivations for engaging these groups, what they should be engaged in, and who should be responsible for engaging them. Moreover, they outlined various complexities and challenges related to engagement. In what follows, this will be discussed in more detail. Relevant quotes are listed in Tables 2 and 3.

Reasons for engagement (Table 2)

Broadly speaking, four overarching reasons to engage communities, stakeholders and publics could be distilled from the interviews. These reasons were not mutually exclusive, and many respondents mentioned several reasons for engagement.

The first reason was that people who would be affected by GDT deployment should be involved in decisions that could (positively or negatively) affect them for reasons of justice. These respondents argued that persons who could be affected should be given the opportunity to contribute to shaping the development of GDTs and have a say in decisions about GDT deployment (Quote 1A). At the same time, respondents had different views on when individuals or groups would be sufficiently affected to warrant their engagement. Correspondingly, respondents used this reason to argue in favor of involving different groups, including communities, (specific) stakeholders, or publics at large. Some respondents also argued that the degree to or way in which groups could be affected should determine in what way particular groups should be engaged, for instance arguing that while a broad range of stakeholders should be engaged, only potential beneficiaries should get a say in decision-making about deployment (Quote 1B). A few respondents mentioned that a fair process in which communities,

16 The terms 'communities', 'stakeholders', and 'public(s)' were defined and used in different ways by the respondents of this study, frequently without explication of or differentiation between these categories. Generally speaking, respondents used the terms 'communities' and 'stakeholders' roughly in line with the way in which these terms were defined in a foundational report on GDTs written by the National Academies of Sciences, Engineering and Medicine (NASEM). According to this report, communities are "group[s] of people who live near enough to a potential field trial or release site that they have tangible and immediate interest in the gene drive project" (p. 180) (4), and stakeholders are "person[s] with a professional or personal interests sufficient to justify engagement" (including communities) (p. 185) (4). Correspondingly, we use these terms in this way in this manuscript. The term 'publics' was used in at least two significantly different ways by respondents. One the one hand, some respondents used this term to refer to what others called communities. On the other hand, other respondents used this term in line with the NASEM definition: "groups who lack the direct connection to a project that stakeholders and communities have but nonetheless have interests, concerns, hopes, fears, and values that can contribute to democratic decision making." (p. 184) (4). Where the term is used in the text of this manuscript, we use the term pubic(s) in the second sense.

stakeholders or publics are engaged in the right way could legitimize its outcome (Quote 1C). What they considered the 'right way' differed among respondents, as is further explored in the next subsection.

The second reason was that engagement could contribute to more responsible development of GDTs or to better decision-making. Respondents pointed out that publics, but particularly communities and broader stakeholders can bring up new viewpoints, questions and concerns that can help reduce blind spots (Quote 1D). The third reason was that engagement could help to ensure that GDT deployment would be acceptable to these different groups and could prevent public backlash (Quote 1E). The fourth reason was that engagement could educate and inform these different groups about the research that is taking place (Quote 1F).

Timing and design of engagement (Table 2)

Engagement can take many shapes and forms, and respondents' views on the timing and design of engagement strategies also depended on how they motivated its importance.

Many respondents considered it essential to engage stakeholders 'upstream', i.e. early on in the research process to ensure GDTs and related governance could still be shaped by their input (Quote 1C/1G). At the same time, it often remained unclear what such engagement should consist of, and respondents had different views on this matter. This can be illustrated by the list of different issues in which communities, stakeholders and publics should be engaged according to different respondents, which included providing input on funding choices, taking part in outreach activities, having access to complaint mechanisms, participating in deliberative discussions, giving approval for each stage of the development of GDTs in stage-gate processes, and deciding about final deployment.

Other respondents focused on the 'downstream' engagement of communities and/or other stakeholders in decision-making about deployment, as such engagement could legitimate the decision to deploy GDTs. On this point, too, respondents agreed on the overall aim, yet different in their views of *how* these groups should be engaged in such decision-making (see 'Theme 3: Decision-making models').

Table 2. Engaging communities, stakeholders, and publics

	(Sub)theme	Quote
	Reasons for engagement	
1A	Engagement of those affected is necessary for reasons of justice	R21: *"The best thing to do is to try to give everybody a chance to have their say. Especially the people that would be most directly impacted by the release of a gene drive in an area. (..) That's really fundamental to doing this. Their environment's going to be altered, their health is (..) maybe placed at risk, so they have to have a say in the release of a gene drive into the environment. There needs to be public engagement too as far as giving everybody with a stake in the gene drive a say in the decisions that are made. That would include obviously people with environmental concerns. But also industry, religious groups, anybody in society that has some stake in gene drives."*
1B	A broad range of stakeholders should be engaged, but the focus should be on potential beneficiaries	R5: *"What we want to do is to engage everyone, but make sure that the centre of the engagement is on beneficiaries and giving them - they can say at the end that they don't want it. (..) [they are] the ones to make decisions."*
1C	A fair process could legitimate its outcome	R22: *"My personal experience is that (..) people who are very skeptical of genetic engineering and think it unlikely that they will eventually support the release and vote in favor of releasing the [gene edited organisms], are still strong supporters of the project because they think that this is how technology should be developed, that you should go to the community and ask the community what they want and invite the community to guide the research and development stage. And so, they support the project even though they don't actually support the idea of genetically engineering [organisms]."*
1D	Engagement could contribute to responsible development of GDTs	R32: *"We need diversity of disciplines, need diversity of world views, need diversity of perspectives to really do this responsibly because there are so many blind spots that will be involved in this really complex technology interacting with ecosystems which are also highly complex, not to mention the political, geopolitical and societal situations".*
1E	Engagement could prevent public backlash	R16: *"In the long run, it might avoid like backlash after, I would say ten years of research and then your innovation is just considered like, no, it's not going to go outside of the lab."*
1F	Engagement could inform different groups about the research	R15: *"The community and the public engagement's really key and those discussions are really important (..) people need to know what they're talking about and understand what they're talking about to actually be – for it to be a meaningful discussion."*
Timing and design of engagement		
1G	Engagement should start in an early stage of the research process	R21: *"I think if you're going to do community engagement, it needs to be done really early on in the process so that it's not a fait accompli. It's not like a thing that's already - a done deal. So the community really feels that they're being heard and they have a say."*

Complexities and challenges of engagement (Table 3)

Respondents also mentioned several challenges for and complexities of engaging communities, stakeholders, and publics. First, various respondents mentioned bias or framing of the provided information on GDTs can unduly influence the engagement process. While several respondents praised the engagement efforts that the gene drive community are undertaking (Quote 2A), other respondents were critical of engagement processes led by scientists, who in their view necessarily have a conflict of interest by virtue of their role in the research (Quote 2B). Correspondingly, several respondents argued that stakeholder engagement should be controlled by an independent third party that has less personal interest in the outcome of the discussion or deliberation. Whilst respondents from the natural sciences did not mention this as a reason to abstain from playing a role in engagement processes, they did bring up their stake in GDTs being successful (Quote 2C). One respondent argued that funders should make funding available for independent parties to conduct engagement processes.

Second, respondents mentioned engagement processes can be time- and resource intensive (Quote 2D). Some respondents also noted engagement of communities and publics can be a challenge due to the complexity of the science (Quote 2E), whereas a few other respondents underlined that it should not be assumed members of the public do not understand science (Quote 2F). Some respondents mentioned that public engagement tools and processes should be adjusted to specific contexts, such as literacy levels, to facilitate understanding. Moreover, a few respondents suggested that people who participate in engagement processes should be compensated for their time.

Third, a few respondents argued that some engagement processes are a farce; they contended that although everyone agrees engagement is important, the input of those engaged is hardly ever taken seriously and/or they are not given true decisional capacity because it is not an integral part of institutions and scientific practice (Quote 2G). Other respondents argued that engagement processes often only focus on the science, whereas they should focus on other aspects too (such as the underlying values, the way in which technologies should be governed, and what to fund in the first place) (Quote 2H).

Table 3. Complexities and challenges of engagement

	(Sub)theme	Quote
	Complexities and challenges of engagement	
2A	The gene drive community handles engagement well	R1: *"I like how it's being handled by the field – that there is a lot of commitment, that stakeholders are actively involved."*
2B	There is a conflict of interests if scientists are responsible for engaging stakeholders	R32: *"[There are no] alternative ways of public engagement [that are] not only run by the technology developer itself, which I believe is an inherent conflict of interest. (..) You have an organisation seeing benefits strongly and risk lower, they are providing information about the technology and they're running the public engagement. That's going to bias the decision-making."*
2C	GDT scientists have a large academic interest in GDTs working	R28: *"I try to separate myself from the theorist and who's proposing something to be done in the real world (..) a lot of theorists would like to see their theory tested. I'm not the person to ask because my name is on the [important gene drive] paper. (..) People talk about conflict of interest in terms of money. (..) I think academics are driven by things other than money. If an academic says: I predict that starlight will be refracted by gravity, or I predict that a gene drive can be contained by daisy-chain, I have a high motivation to test that prediction, possibly a higher motivation than: Oh, you're going to get $1-billion if the gene drive works. Academics don't need much money, most of them don't have expensive hobbies like collecting cars, they have expensive hobbies like collecting centrifuges."*
2D	Engagement processes are time and resource intensive and can be too demanding	R28: *"And the problem with inclusion of public isn't that scientists don't want to include the public, it's the public doesn't want to be included. It's boring. It's time consuming. They've got a day job, you know, it's very hypothetical."*
2E	There needs to be a certain level of understanding for informed deliberation to take place; this can be a challenge	R33: *"And frankly, informed deliberation is the key. (..) You have a difficulty because at the very local level there's a question of education, at the national level there's also the question of developing sufficient capacity for evaluation and assessment. (..). Informed consent requires an understanding of the technologies, environmental effects and health benefits and it is going to be difficult to expect a family (..) to fully understand the range of issues. (..) Developing a (..) capacity for engagement on these issues is something that's necessary, but that takes time."*

Table 3. Continued

	(Sub)theme	Quote
	Complexities and challenges of engagement	
2F	It should not be assumed that people do not understand science	R13: *"We shouldn't presume that people are ignorant of science. Actually, people buy into science, use scientific language, medical language to assert credibility and to show that, you know, they do their own research about you know, what is the science, so we shouldn't presume that they do not know what gene drive is and we are going to fill in the gap. But it's all the stuff with public understanding of science. That's a bit of what happened with GMOs [genetically modified organisms], presuming that people don't know. (..) people do research and often become experts."*
2G	Some engagement processes are a farce as these are not embedded in institutional structures	R22: *"The typical person - when approached with this question of if you're developing a technology to change the shared environment, should you go and talk to the people who live there first and ask them what they think about it and which version of the possible technological options they would prefer? Is that the right thing to do? - Everyone says "yes", everyone says "it's wrong to keep it a secret and just develop something that's likely going to be forced down their throats later on", and everyone says, "It's wrong to deny people a voice in decisions intended to affect them, that they won't be able to opt out of". (..) Everyone seems to agree with this point, it's just that's not enough to make institutions change, it's not enough to change the incentives of science"*.
2H	Engagement should not just focus on science, but also on values	R17: *"We are testing the way that society thinks about this. And during that process there is a public consultation. But publics are only allowed to talk about science. They're not allowed to talk about these other aspects [the different values that are at play in risk assessment]. And there's been a push for a long time or a recognition for a long time that that's insufficient, that we need to open that space out somehow. But there is no model for doing that and we've failed to achieve that in Europe and in North America. And now for some reason we think we can do that Africa with this gene drive mosquito."*

Theme 2: Power dynamics

Another prominent theme in the reflections of respondents related to the power dynamics that may be present in relation to GDT research and deployment. Respondents stressed the importance of not repeating historical injustices regarding decision-making in LMIC, and recognized various dilemmas that researchers face in view of these issues. In what follows, these considerations will be explored in more detail. Relevant quotes are listed in Tables 4 and 5.

Power dynamics in partnerships between HIC and LMIC (Table 4)

Many respondents commented on the potential power imbalances that may be present if scientists from HIC develop GDTs for potential deployment in LMIC. Various respondents argued it is essential to prevent repeating the longstanding precedents of unjust decision-making in the global South by people from the global North[17] (Quote 3A), for instance during the colonial period, in the governance and decision-making about GDTs. Some respondents commented that they considered it problematic if these technologies were developed by scientists who do not live in the region where GDTs may be deployed for the first time because risks may be perceived differently when one is not subject to them oneself (Quote 3B).

Respondents also suggested various ways to mitigate these issues and concerns and

17 It should be acknowledged that concepts used to divide the world also oversimplify it (63). Where we use the terms 'global North' and 'global South', one may also read 'Minority World' and 'Majority World' – terms that do more justice to the fact that the largest share of the world population is located in the global South.

stressed the duties of researchers in this regard (Quote 3C). Most importantly, various respondents said that the inclusion of local communities, scientists, or organizations in the development and/or decision-making about these technologies can help mitigate these power imbalances (Quote 3D; see also Theme 1). Similarly, some respondents argued it is important to support and strengthen the local infrastructure so that different countries could independently govern GDTs (Quote 3E). One respondent argued this is indeed what is being done in Burkina Faso, and that this is thus not at all reminiscent of colonial practices (Quote 3F). Another respondent, in contrast, argued that power is not actually being redistributed in local engagement practices in some countries where GDTs are currently being developed, and that it should be checked whether the language of co-development is brought into practice (Quote 3G).

Table 4. Power dynamics in partnerships between HIC and LMIC

	(Sub)theme	Quote
	Power dynamics in partnerships between HIC and LMIC	
3A	It is essential to prevent repeating the long-standing precedents of unjust decision-making in the global South	R27: *"[A risk related to deployment of GDTs could be] repeating a precedent that we've set many times in history allowing small groups controlling a powerful technology to just force it on the rest of the world. Only in this case we're doing it at a global scale much more rapidly. I would say that's an existing risk. It's unfortunately been a part of human history too often. And I'd rather set a precedent that is opposite [to that] rather than repeating my predecessor's mistakes."*
3B	It is problematic if GDTs are trialed elsewhere since risks may be perceived differently if one is not subject to them oneself	R2: *"I think it's strange that we're talking about a technology that may be deployed in Africa. Although it'll be discussed and deliberated there, it remains a Western technology that we'll present there. (..) we develop a technology of which we're not sure, like, is it sufficiently safe, but we think we may deploy it in an area where we don't live."*
3C	Scientists should think about their intentions and how they approach foreign communities	R25: *"In general and in countries with a colonial past, you obviously have to be very careful when you approach people, with all your good intentions. And of course, you should ask yourself: 'to what extent do I have a missionary zeal, and is that legitimate, and how will that come across? (..) how do you work, how do approach and deal with people, and to what extent do you really respect people as they are?"*
3D	Inclusion of local communities, scientists and/or organizations can help mitigate these power imbalances	R29: *"There is a strong history of global North countries making decisions that heavily impact countries and communities in the global South. Rather than perpetuating patterns of colonialism, extraction of resources which are not ours, the approaches to address public health and conservation issues need to be community driven, they need to be approaches which are supported by and are healthy for frontline communities."*
3E	It is important to support local infrastructures so that countries can independently govern GDTs	R25: *"I think the ideal scenario (..) and the one in which you have the best control over, let's call it, colonialist tendencies, [is] that you (..) strengthen the scientific infrastructure regionally. And that you help with, ultimately that researchers, scientists and public health authorities in the countries themselves can take control, that they can implement the technology themselves."*
3F	Lo scientists are involved in the development of GDTs in Burkina Faso; this is not reminiscent of colonialization.	R7: *"I saw an article in a paper saying that now you know Europe or you know US now, they have a new way of colonizing Africa. (..) This is something like, okay what do you mean? There is a technique, so the technique should stay somewhere and we as Africans, we should not try that? If we say okay this is something that we're gonna try, we´ re gonna work on that and [people] say yeah well it´ s colonization. [But] we also studied with so many people that are involved in the project and they did post-docs in the US and they had experience. So they know what they are doing. So it´ s crazy [to consider it a new way of colonization]".*
3G	It should be kept in check whether power is actually redistributed	R17: *"There is a language being used, the language of co-development (..). this is a language which is coming from the UK in a very sort of strategic way. (..) I'm more sceptical of the real kind of sharing of power that might be going on, that there's potential for but isn't actually happening yet."*

Dilemmas related to power dynamics (Table 5)

Respondents also reflected on whether and to what extent (foreign) researchers can legitimately make demands regarding local decision-making procedures. On the one hand, some respondents argued that researchers should accept the local culture and norms and adopt local decision-making procedures (Quote 4A). If they demanded alternative decision-making procedures, a few respondents argued, they could rightfully be accused of colonialism (Quote 4B). Slightly deviating from this perspective, another respondent argued that although local decision-making procedures should broadly be followed, foreign researchers could justifiably set minimal thresholds, for instance to ensure a certain level of inclusion of women and minorities in decision-making.

At the same time, various respondents recognized that the obligation to respect local governance and decision-making structures could create tensions with the co-existing obligation to engage those affected. Some of these respondents expressed concern that GDT deployment could be considered in settings in which legitimate decision-making process is not guaranteed, for instance in countries with a government that does not respect its citizens' rights (Quote 4C). A few respondents mentioned that they considered some of these concerns relevant to ongoing GDT projects (Quote 4D). Respondents also commented on the implications for (decision-making about) potential GDT deployment. Specifically, several respondents argued that GDT research could be considered unethical if it was conducted in a context in which the conditions are not right for adequate protection and engagement of affected people (Quote 4E). Several other respondents argued that it would be preferable to conduct the first field trial with GDTs in a setting with low levels of poverty and existing participatory decision-making structures to mitigate concerns about exploitation (Quote 4F).

Respondents also reflected on the dilemmas these difficult tensions create. Some respondents stressed that some countries or regions with fragile political systems are also hit the hardest by vector-borne diseases, and therefore the need to consider GDT deployment is highest in these areas (Quote 4G). Other respondents remarked that not testing new technologies in areas with 'vulnerable' populations may in fact make these populations more vulnerable, for example because the status quo puts these populations at increased risk of disease (Quote 4H). One of these respondents stressed the importance of accountability in research settings with a fragile political structure and high levels of poverty. According to this respondent, it could be justifiable to carry out research in such settings as long as the researchers could give a good account of why a particular location was picked, why research was conducted in a particular way, how local communities and policymakers have been involved, and how obligations to the community have been fulfilled. Finally, several respondents commented that it is important for GDT projects to invest in and support capacity building to prevent or mitigate these concerns where applicable (Quote 4G).

Table 5. Dilemma's related to power dynamics

	(Sub)theme	Quote
	Dilemmas related to power dynamics	
4A	Decision-making processes should be in line with the local culture and norms	R31: *"[The design of community consent and authorization processes should] be very dependent on the local culture and the local norms. (..) If that's the way they make collective decisions then that's the way the collective decision should be made. The important thing, of course, is you try to reach out and provide information to all the different components of the community and so it shouldn't just be guys in the circle making a decision. It seems, at least at this point in time, the right thing to do is to go to the community and ask: 'How do you make these decisions, what's your way of doing it?' and then do it that way."*
4B	Researchers should be careful with demanding alternative decision-making procedures	R25: *"You might look at how they decide about spraying insecticides on a large scale. (..) Who decides that? Does every community member decide that? Do the village elderly decide, or does the health ministry just send a DDT spray crew? (..) While that does not justify the process, it does not make it legitimate or defensible in any absolute way (..) it is something you should take as a given. And then the question, then, is to what extent if you say "actually, everyone in the village should agree to that", where you get the legitimacy to [say that]. Because then you will of course soon be accused of colonialism. Then you do indeed arrive at a (..) potential culture clash about the ideology of decision-making."*
4C	GDTs could be considered in countries in which a legitimate political process is not guaranteed	R10: "*I worry about research being done in a place where people don't have rights, don't have their rights respected and in places where it would be very difficult for people to say no. (..) That might have to do with political structures that don't mean that people get respected, but another reason might be just extreme poverty and a research that doesn't take its responsibilities to communities seriously*."
4D	In Mali, there is no sense of being able to express criticism	R17: *"So Target Malaria [a non-profit research consortium that develops GDTs for malaria control] at the moment is working very much on the informed consent of communities, developing those relationships. That's part of what the GM [genetic modification] mosquito release in Burkina Faso is and they'll be doing the same thing in Uganda and the same thing in Mali. (..) in Mali, there is no sense of being able to critique. There's no possible critique of gene drive (..) To be fair, I think part of that is driven by the fact that malaria is a very serious problem and the potential to eradicate malaria is really, you know, it's enviable and highly desirable by (..) I would think everybody in Mali. (..) that's a pretty agreed on target. How you get there is another matter and I think if you want free and informed consent (..) there needs to be an awareness, a free and informed decision-making process."*
4E	GDT research and/or deployment would be unethical in a context in which the conditions aren't right for people to be adequately protected and involved	R25: "*In the end you can get to a point (..) [at which] you reach the limit of what you consider acceptable conditions under which to carry out your projects, to do your research, with which you obviously withhold a population the probable chance of a successful control of that vector. If you say, well, this dictatorship, we're not going to carry out our project here – yes, of course that means that local people are withheld that opportunity. And if your commitment is actually to help those people, yeah, then what should you choose? (..) you really need to take a case-by-case decision based on the expected chances of success, the responses you gauge from a population, and (..) the nature of the regime. I can imagine that there are regimes you don't want to have anything to do with, and that that would be legitimate*".
4F	It could be preferable to pick settings with low levels of poverty and existing participatory decision-making structures to mitigate concerns about exploitation	R33: "*In some ways I actually believe that it would be kind of nice if the applications were to human health on Martha's Vineyard in Nantucket. You know why? No one can say that you're exploiting a poor population to experiment on them because Martha's Vineyard in Nantucket are the richest areas of the country. (..) you also have high educational levels, high incomes, a functioning form of government town meeting with pretty broad participation. So (..) work in those settings I think sets an example of non-exploitative engagement.*"
4G	The need for research and interventions is greatest in countries with unstable political systems or vulnerable populations	R31: "*We always hear these criticisms about starting in Africa because people are worried the decision-making capacity is not there. It's incumbent on those who are supporting this technology to make sure it is there. I mean, the rationale for starting in Africa is not because you can get away with murder there, the rationale is because we're trying to address and interact with a problem there.*"
4H	Not doing research in areas with vulnerable populations may also make them more vulnerable	R10: "*You know, there are fragile states of one kind or another so it's not straight forward. I'm also weary (..) of the idea of not doing research on populations simply because they're vulnerable. I think that's potentially a way of make them more vulnerable. (..) A good example would be research with pregnant women, that kind of thing. We've spent so long kind of avoiding that, that actually in the end pregnant women don't get the kind of treatment that are designed for them so they're worse off anyway. That doesn't mean you should just go and do anything you want with pregnant women or with people in poor countries, but it does mean there are special responsibilities in those kind of contexts I think. So, it's hard.*"

Theme 3: Decision-making

A third prominent theme in the reflections of respondents related to the governance structures that should be in place to make decisions about GDTs and their deployment. In what follows, these reflections are discussed in more detail. Relevant quotes are listed in Tables 6 and 7.

Comparing decisions about GDTs to other area-wide interventions (Table 6)

A first point of difference between respondents related to whether decisions about GDTs should be made in the same way as decisions about other environmental interventions or not, which in turn depended on whether they viewed GDTs as having exceptional characteristics. Broadly, four different positions could be discerned.

First, some respondents contended decision-making about deployment of GDTs should be consistent with decision-making about other area-wide environmental interventions. These respondents did not consider GDTs to have unique characteristics that warrant specific governance structures. Within this group, some respondents argued that they did not see any grounds to deviate from commonplace decision-making procedures that are currently used to make decisions about other interventions that could potentially affect a wide area, such as nuclear power plants (Quote 5A). Other respondents in this group agreed decision-making about deployment of GDTs should be consistent with decision-making about other area-wide (environmental) interventions, but argued that the way in which decisions are currently made about interventions in our shared environment is generally inadequate and should thus be improved for all such interventions (Quote 5B).

Second, some other respondents took an opposite stance, arguing that decisions about GDT deployment cannot be made in the same way as decisions about other environmental interventions. These respondents contended that the self-propagating character of GDTs makes them unlike other area-wide interventions because of their far-reaching, unpredictable, and negative impacts and consequences (Quote 5C) and argued that there is no adequate governance system in place that is apt to decide about technologies with such characteristics (Quote 5D). On these grounds, these respondents argued in favor of a moratorium on GDT deployment. Other respondents argued against a moratorium because they considered it an overly cautious approach in which the potential benefits of GDTs cannot be investigated (Quote 5E). Some others argued a moratorium is unrealistic (Quote 5F) or would create false reassurance if it was a voluntary agreement amongst different parties (Quote 5G).

Third, many other respondents agreed GDTs have certain unique characteristics (such as the impossibility of opting out or the level of uncertainty and risk involved with their deployment) compared to other environmental interventions, yet argued this warrants the development of novel or additional governance mechanisms rather than a moratorium. For instance, several respondents mentioned more stakeholder input on GDT decision-making is warranted than is usually the case for other environmental interventions. Moreover, some respondents argued any GDT research should undergo a regulatory check before it is executed (Quote 5H). Additionally, several respondents mentioned measures that should be implemented to increase regulatory control over GDT research, including a registry of GDT experiments (Quote 5I), more surveillance, and a whistle-blower encouragement system (Quote 5J) to flag any suspicious research.

Fourth, some respondents argued that decision-making about GDT deployment would pose unique challenges as this could affect a very large number of countries, parties, and individuals, but argued this issue should be resolved by adapting the technology rather than the decision-making procedures. They argued in favor or developing localized or threshold-dependent GDTs that are spatially or temporally limited in their spread rather than non-localized GDTs intended to spread throughout a population or species. Several respondents argued that they considered localization a necessary condition for a first deployment of GDTs because this would, in their view, be the only way to overcome or sufficiently mitigate these decision-making challenges (Quote 5K).

Table 6. Comparing decisions about GDTs to other environmental interventions

	(Sub)theme	Quote
	Comparing decisions about GDTs to other environmental interventions	
5A	We can use the same governance mechanisms for decisions about GDT deployment as for other area-wide environmental interventions	R8: "*We do manage [to make decisions about other area-wide or community interventions]. (..) We do manage to talk about fluoridic water and clean air and - not, you might say, not very effectively, but nonetheless (..). And we occasionally manage to build roads and sewer plants and once in a blue moon nuclear power stations. (..) You can try, you know, terms like direct democracy and referenda (..)..That is not how we normally do things, that is not how we decide whether to give planning permission for a new housing estate, put in a new road, a sewer, a bypass or any other multi-person infrastructure thing. That's not how we do it. We do some sort of representative democracy, so we have local representatives (..) do that stuff. What's the difference? (..) So you could just say just ask the [entity that has] authority for whatever it is. (..) If they say yes then you're done. The bar has usually been, for GM mosquito stuff and probably new technologies in general, has generally been set quite a lot higher than that.*"
5B	The way in which we generally decide about interventions in our shared environment is not adequate	R21: "*I lived in a community (..) where routinely there was mosquito spraying. (..). There were trucks that went down the alleyways in the summertime and sprayed a bunch of pesticides. And I don't think I ever got to vote on that. It was just a mosquito control board whoever was in charge, she got to say whether this was a good thing or not. (..) I don't feel so good about [that]. I really do think I should have had more of a vote or maybe I should have at least had more awareness of the ability to (..) give input to the board.*"
5C	There should be a moratorium because of the potentially negative and irreversible consequences of GDTs	R29: "*Gene drives are designed to drive a particular trait through an entire species and could have far-reaching and unpredictable, negative impacts and consequences for organisms and the environment. This technology has raised a number of red flags regarding its potential applications in agriculture, for use in bioweapons, its potential use in conservation. (..). That's why (..) we need an international moratorium on the use of gene drives for release into the environment or into agriculture.*"
5D	There should be a moratorium because we need to develop a fair regulatory system	R32: "*I'm not anti-technology in any way, I'm anti only certain people getting to decide how it gets used. Again, I think there needs to be maybe some more space for just reasonable reflection on what we're really dealing with and what needs to maybe be in place to safeguard it because everything is inadequate right now: the technology's not ready, the regulatory systems are not ready, the input from the public isn't ready. There's just so much that's still missing.*"

Table 6. Continued

	(Sub)theme	Quote
	Comparing decisions about GDTs to other environmental interventions	
5E	A moratorium is an overly precautious approach	R12: "*The reason I'm against the moratorium is that I think we ought to push back a little bit against this overly precautious approach. (..) I think in order to make an informed decision about whether we should be doing field trials or more general releases, we really need to know a lot more about what the technology can and can't do. And so we're kind of, to issue a moratorium now would just be making a choice in the dark. And I think that the potential benefits are far too great to make that kind of uninformed choice.*"
5F	A moratorium is unrealistic, so we should focus on ways of doing this as safely as possible	R33: "*People that say (..) we oppose extinction drives, we don't want to be seeing research in this area, we want to be seeing prohibitions indefinitely on release, I want to say: it's unrealistic. I cannot image India standing for that position when people are dying of malaria. And India has the technical skills to be able to do it quickly. (..) I don't want to be saying 'just because someone's going to do it, stop talking', no, but I'm saying if you hold out with too stringent a set of conditions it's going to happen. So let's get together and focus on ways of doing this as safely as possible.*"
5G	A moratorium would offer false reassurance	R28: "*Almost every time I bring up surveillance it's usually because a bunch of academics are posturing that all we have to do is sign a document: Let's get a lot of signatures on this document where we have a moratorium and it will be a voluntary moratorium. And, in fact, they're very thrilled that it's a voluntary moratorium, and I say: 'Come on, man! We've got an involuntary moratorium on introducing wild species because of the EPA, and on introducing pharmaceuticals because of the FDA, why do we need a voluntary one on top of that?' (..). The moratorium is (..) just like a false reassurance. What we want to do is stiffen up with things that are involuntary, that are regulated.*"
5H	Any GDTs should undergo a regulatory check before it is executed	R2: "*The [regulatory] system in the Netherlands used to be set up in such a way that if you are allowed to do work at the lowest [safety] level, you don't have to register for it every time. So, if you already had permission to work with CRISPR-Cas and you thought, I'm going to turn that into a gene drive, [the regulatory authorities] wouldn't see that. When we realized this, it was immediately – alarm bells, we have to do something about this. Then we specified that if certain conditions are met (..) you need to apply for a permit. Then it comes to the attention of the authorities, so to speak, and then a risk assessment can be done that considers all kinds of issues.*"
5I	There should be an (international) registry of GDT experiments	R20: "*I think one pre-condition [for GDT field trials] is that (..) there should be transparency, I think that's very important. So in human genome editing there's a lot of discussion about the need for registering for the experiments in international database, so that everyone knows what's going on. And I think there could be similar efforts in this area.*"
5J	A whistle blower encouragement system should be set up to flag suspicious research	R28: "*In addition to surveillance we need consequences. You need a whistle-blower encouragement system: if anybody sees something, they should be encouraged to say something. How do you do that? This came up with the CRISPR babies. A lot of people who knew about the CRISPR baby project and they didn't say anything to anybody other than to the person doing the experiment: Don't do that. (..) You've got to do more than that (..).*"
5K	Localization is a necessary condition for a first field trial or release	R26: "*First field trials for sure need to be like a localized drive. We need to do quite a bit of testing. And you've got to do it in a controlled way so localized it is, because that way at least you don't need pan-continental agreement.*"

Decision-making models (Table 7)

A second point of difference between respondents related to the decision-making models that should eventually be used to decide about GDT deployment, with different respondents proposing different decision-making models to achieve this.

One respondent suggested that individual informed consent to GDT deployment is warranted (Quote 6A). In contrast, multiple other respondents noted that individual informed consent is not suitable for public health interventions such as GDTs (Quote 6B). According to some of these respondents, individual informed consent would only be required if the people involved could be considered research participants (Quote 6C). Moreover, respondents pointed out that it would be unjust to apply individual informed consent to public health interventions such as GDTs because it would allow individuals to trump the needs of the collective (Quote 6D). Finally, various respondents remarked that it would be practically impossible.

For these reasons, almost all respondents were in favor of obtaining consent on a community level (Quote 6E), yet they differed in their views on how such a community consent process should be shaped. Several respondents commented that they considered direct democracy approaches[18] based upon a majority rule problematic because this would not allow minorities to have sufficient influence on decision-making (Quote 6F) or because such approaches are prone to be influenced by mere sentiments (Quote 6G) such as an uninformed fear of the unknown. To counter this, various respondents were in favor of using deliberative democracy approaches, in which a final decision would be preceded by deliberation, as this would facilitate more in-depth reflection on different arguments and would allow more diverse viewpoints to be taken into account (Quote 6H).

A few other respondents argued that indirect decision-making by representatives would be best because people would not have the background and time to make an informed decision about such a complex issue (Quote 6I). Finally, several respondents stressed it should not be either/or; there should both be agreement by or consensus of the relevant transnational organization(s) (such as the African Union (AU), the New Partnership for Africa's Development (NEPAD), and/or the World Health Organization (WHO)) as well as some form of community agreement or consent.

Table 7. Decision-making models

	(Sub)theme	Quote
	Decision-making models	
6A	Individual informed consent is warranted	R29: *"Applications are interesting as intellectual exercises but we really need to think about the technology platform of this extinction technology: (..) Who's making the decisions? Where are the global, international regulations and assessments? Who needs to give consent? If this is a technology designed to drive across all borders and boundaries then everyone affected needs to give their consent and that means everyone."*
6B	Individual informed consent is not suitable for public health interventions	R22: *"Informed consent is something that maybe appropriate for medical ethics, but it is not appropriate for public health and no one has ever suggested seriously that it is."*
6C	Individual informed consent is only necessary for research participants	R31: *"Individual informed consent would only be required for people who actually meet the standards of human subject research."*
6D	Individual informed consent is undesirable for public health interventions	R8: *"And it's also difficult, I mean, another thing that comes up in this area (..) is the deliberate confusion [by anti GM activists] between this sort of area-wide technology and an individual based medical trial (..) or intervention. (..) The argument then is if somebody is going to be in the area of GM mosquito release then that's an experiment on them, which is not really true, but let's say, and you need their individual informed consent. OK? Or you can turn that around and say that means that everybody in the release area should have an individual veto on this collective action. Which (..) is incredibly anti-democratic."*
6E	Consent should be obtained on a community level	R12: *"We don't think that individuals just need to be informed about what's happening, they need to provide active consent to it. Now obviously that's going to be much more difficult in a public health context or in the context of a GMO [genetically modified organism] environmental trial because you can't necessarily go around knocking on everyone's door and asking if they want to have this trial or not. But I think there are certainly political procedures you can use to try and get something more closely approximating community consent."*

18 I.e. approaches in which people would have a direct say in whether GDTs are deployed or not, for instance through voting.

Table 7. Continued

	(Sub)theme	Quote
	Decision-making models	
6F	Direct democracy approaches based on majority rule are undesirable for they do not give enough space to minorities	R3: *"I do not like democracy by majority rule. (..) Democracy is that all minorities get space. Not just to exist, but to express themselves and to influence policies. The majority rule is an emergency procedure. We can't figure it out, so we'll resort to voting."*
6G	Direct democracy approaches are undesirable for decision-making for they are prone to be influenced by mere sentiments	R4: *"I do not think it is realistic to say that we should all decide together, that it should be a democratic decision, because then you get something like Brexit. That was very important, yet people voted based on all kinds of sentiments, that may not have overseen what the consequences would be. And well, that would, you would also run that risk if you, for example, you were going to hold a referendum on this, about whether we do or do not want a gene drive."*
6H	Decision-making should be based on deliberative discussions with diverse voices	R10: *"You have to pay special attention to making sure that, and this is where it moves into sort of the deliberative democracy kind of space (..), you have to pay particular attention to the sorts of people who usually get excluded from those discussion. You have to pay particular attention to diversity of voices and it's really important to pay attention, deliberately seek out people who are critical and to make sure there is a proper discussion on that. So it's not to say that they should get any special kind of weight necessarily but to have a process of discussion that takes difference seriously and probably includes it."*
6I	Decision-making by representatives would be best	R8: *"Most people, most of the time aren't going to take the time to look at those arguments and figure out what is what. And possibly don't have the general science, whatever, background to do that. And so most people will trust other people to do it for them. (..) so, you know, the sort of trusted intermediate thing, which might be national academies or regulatory bodies or whoever it is, you know, the government (..). This is actually how most things work."*

Discussion

To our knowledge, this is the first in-depth qualitative study focused on professional experts' perspectives on GDT governance. Three main themes were identified, relating to (1) engagement of communities, stakeholders, and publics; (2) power dynamics, and (3) decision-making. In what follows, we relate our findings to the broader literature, and highlight issues that have thus far been underrepresented or underexplored.

The challenge of moving from general moral principles to concrete obligations

In line with the GDT literature (4,20,22,23,25,38), there was broad agreement amongst respondents on the importance of engaging communities, stakeholders, and publics. At the same time, the interviewed experts had divergent views on what this should consist of. To some extent, the different views may not be incompatible: different stages of technology development and contexts may warrant the engagement of different stakeholders, in different ways and for different reasons (10,38–41). However, the broad variety of views also points to underlying, unresolved normative questions with regards to their specification and operationalization.

As philosopher Stephen Toulmin already outlined in his reflections on the Belmont Report's principles for biomedical research ethics (42), it can be surprisingly easy to settle on general moral principles, but much harder to reach consensus on how these should be operationalized. The real challenge, then, lies in specifying these general commitments to concrete moral obligations that stipulate which actions should be conducted or avoided and where, when, why, how, by what means, to whom, and by whom (43). This challenge has also been recognized in relation to engagement in the GDT literature (4,6,7,10,14,22,44). Correspondingly, various authors have argued that an authorized organization should develop official engagement guidelines for GDTs that field studies could be audited against (6,7,22). The results of this study underline the importance of such calls, and point to specific issues that should be addressed in such guidelines and in project proposals of research consortia working on GDTs more generally. Several of these issues are discussed in more detail in what follows.

Ways forward: open questions and concrete recommendations

A first question that should be explored in more depth includes when someone could be 'affected' by GDT deployment in a way that demands their engagement – in other words: when are individuals sufficiently 'affected' and when do they have sufficient 'stake' or interests to be considered communities or stakeholders that should be engaged? (4) It has been argued that a broad conception of interests, that extends beyond human health and safety and includes the way in which people conceptualize their relationship to nature, should be adopted to assess who could be affected by field trials and should be engaged (10). It remains underexplored, however, what these interests should consist of, to what rights and obligations they give rise, and how this should feed into governance. This question is all the more important given that GDTs are designed to spread, which means that non-localized drives in particular could affect a large number of individuals and groups (38).

A second issue relates to how the challenges of such engagement should be approached. An important challenge noted by respondents in this study as well as in the broader literature on engagement is the tension between its demandingness – for instance in terms of its time- and resource-intensiveness for both researchers and participating stakeholders, and in terms of overcoming power dynamics – and its inclusivity (45). The risk exists that a trade-off is made in which engagement is either tokenistic as a result of its demandingness or unfair as a result of its lack of inclusivity. Notably, this tension may be largest in contexts where engagement would be of greatest benefit, for instance in cases where those that could be impacted by the research lack power to influence it or when the distance between their expertise or values and those of the researchers is greatest (45), as could be the case in the context of GDT research. This underlines the necessity of stipulating what engagement aims to achieve, so that engagement strategies can be tailored to achieve those goals in a meaningful and inclusive way. Another challenge is the conflict of interest that researchers may have if they are the ones in charge of designing and conducting engagement. The gene drive community deserves praise for their efforts to go beyond what regulation requires of them in terms of engagement, yet the development of an independent, detailed guideline for engagement could avoid the semblance of a conflict of interest.

A third issue that should be addressed are the power dynamics that are involved in GDT research. Power dynamics may be present in any research context, yet warrant particular attention given the fact that GDTs are most likely to be deployed in countries where large social and economic inequalities exist between the different stakeholders involved and where historical injustices may still affect the way in which knowledge is produced and foreign 'aid' is perceived (4,9,46,47). As the global health, co-production and community engagement literature underline (48–52), such inequalities and histories can contribute to power disparities that could threaten the proposed ideals of co-development and 'fair partnership' between GDT developers, communities and regulators (25). Real-world guidance on how to achieve true engagement and partnership in the context of these and other power dynamics is key to prevent these commitments from remaining tokenistic. Concrete ways to counterbalance power dynamics in research collaborations include explicit acknowledgement of past and present inequalities, setting research agendas in collaboration, clarifying roles and responsibilities, sharing of property rights and resources, and fair representation in authorship (7,47,51,53,54). In interactions with communities and other stakeholders, power dynamics may moreover be mitigated by appointing independent moderators in deliberations and engagement activities, conducting research to tailor educational material and engagement strategies to diverse groups, allowing sufficient time for deliberations, and giving communities and/or other stakeholders formal power (10).

A final issue that should be explored in more depth, and that has thus far been underrepresented in the GDT literature, relates to the demands that foreign researchers may justifiably make on the way in which decisions about GDT deployment should be taken. What demands would constitute a safeguarding of important research ethics standards and rights, and when would such demands turn into cultural imperialism? While potential tensions between devising minimal criteria for responsible GDT governance and respecting local customs, social and political circumstances, and decision-making procedures may exist, several concrete recommendations can be made besides conducting GDT trials in HIC (14). First, this tension could be reduced by ensuring that local rather than foreign experts are in the lead in knowledge production and decision-making. The literature on GDT, and this paper is no exception – both in terms of its author list and in terms of the respondents interviewed – is mostly dominated by authors from HIC, which reflects the current reality that development of GDTs primarily occurs in these countries (25,44). This underlines the importance of evaluating who participates in the development and conduct of research on GDTs and on what basis of equality (44,50,55). Second, when it comes to specific governance mechanisms and decision-making models, this tension may provide reason to predominantly focus efforts on explicating the *goals* that such mechanisms and models should achieve, rather than the specific shape they should take.

GDTs as governance anomalies?

The results of this study also point towards the need to evaluate the way in which decisions about the development and deployment of GDTs relate to broader discussions about the adequacy of governance systems for emerging biotechnologies. As has also been shown by Sam Weiss Evans and Megan Palmer, stances on whether GDTs should be considered anomalies in governance systems are closely tied to stances on whether these broader systems are adequate or inadequate in the first place (56).

Next to stressing the relevance of broader reflections on whether biotechnology governance is suitable and for whom (56), these different stances also invite more in-depth reflection on what it is (if anything) that makes the development and deployment of emerging biotechnologies categorically different from other interventions that may affect (the world around) us, and/or GDTs different from other biotechnologies and area-wide interventions. Emerging biotechnologies more generally may for instance be seen as requiring (more) engagement of communities, stakeholders and publics than other environmental interventions due to their inherent uncertainty and ambiguity, the remoteness of bodies such as research councils from traditional channels of democratic accountability and/or the long timescales between the development of a technology and the realization of its impact (8). Compared to other emerging biotechnologies, for which a concern can be that they *might* spread, a distinguishing feature of GDTs could be that they are *designed* to spread. The most important question, in turn, is what governance measures are warranted in view of such differences. Only by pinpointing and critically reflecting upon these differences can specific governance modifications be proposed to deal with these unique characteristics. This is both important for procedural validity and fairness, and to deal with the earlier described challenge of demandingness in a broader context of research on emerging biotechnologies. As one of the respondents phrased it: "You can't have a deliberative democracy every time you do a research project" (R10).

Limitations and recommendations for further research

As reported in another manuscript based on the same study (16), there are several limitations that should be taken into consideration when interpreting its results. First, our study was the first large and in-depth interview study on professional experts' perspectives regarding GDT governance. Correspondingly, it had an exploratory character to allow experts to bring up issues they considered relevant. Although saturation was reached on the identified codes and themes, further research should explore these topics more extensively. Second, any qualitative research is subject to interviewer and researcher bias; a different interviewer could have focused on other aspects during the interview, and another research team could have grouped the codes and themes differently. Third, our study represents a group of GDT experts that had prominently contributed to the academic and/or policy debates on GDTs. While these experts offered a diverse range of perspectives, they were predominantly employed in the global North, as was discussed previously. Subsequent research should center on the perspectives of experts in other countries, especially those in which GDTs may be deployed, who possess unique expertise on the local context of potential field trial locations that is essential for robust and legitimate governance. This is particularly important with regards to the topic of power dynamics – a theme that was not envisioned in advance, and for which more extensive reflection by experts from countries where GDTs might be deployed is indispensable. Similarly, it would be very relevant to conduct a qualitative study amongst the communities living in areas where GDTs may be deployed who possess experiential expertise that is highly relevant to GDT governance. Finally, many of the issues identified in this study warrant a more detailed normative analysis.

Conclusion

GDTs elicit diverging moral views on whether and how they should be deployed. This ambiguity and the uncertainty related to GDTs make it particularly difficult to make governance choices based on the potential outcomes of their deployment, underlining the importance of procedural fairness in governance mechanisms. This article provides a contribution to responsible guidance of GDT development and deployment by investigating professional experts' perspectives on GDT governance. The obtained insights give rise to specific recommendations with regards to engagement, mitigating power dynamics and evaluating decision-making models, and point to unresolved normative questions that should be addressed to move from general commitments to concrete obligations.

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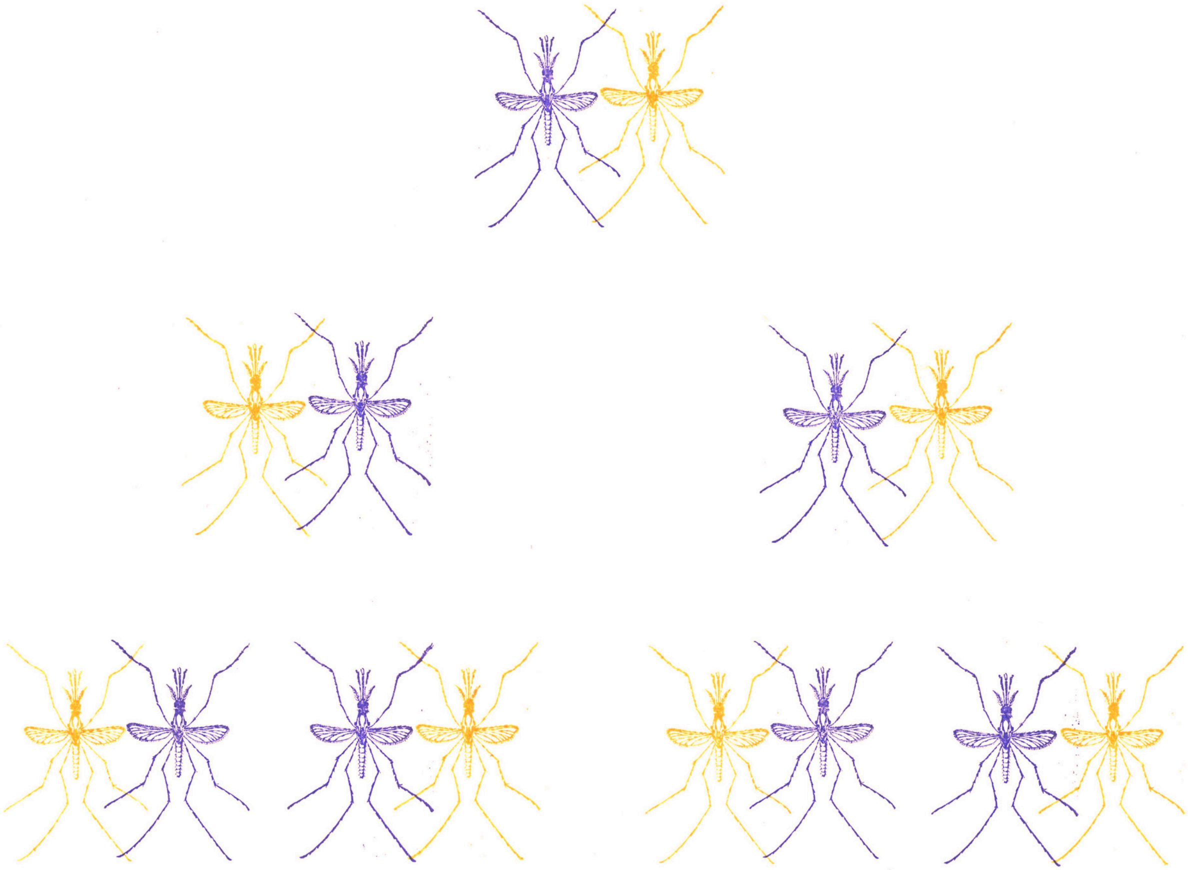
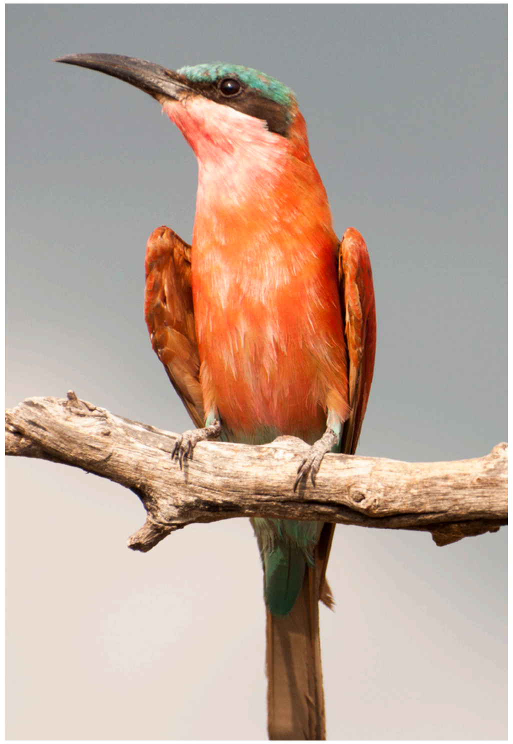


5

PICTURING DILEMMAS OF TECHNOLOGICAL CHANGE: GENE DRIVE TECHNOLOGIES

Nienke de Graeff

Studium Generale TU Eindhoven. November 2019.



5






Gene drive technologies

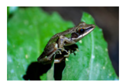
Imagine what could happen if this Malaysian frog would accidentally enter a ship, end up in southern Africa, and turn out to be toxic for these native bird species, threatening their existence?

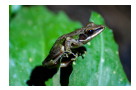
Whilst this is a hypothetical example, the (planned) introduction of cane toads in Australia had precisely these effects. Despite investments of billions of Australian dollars in eradication campaigns the attempts to curtail their invasion have been unsuccessful. In recent years, so-called 'gene drive' technologies are being developed that can be used to reduce the fertility of a species or to alter sex-ratios to limit their reproduction.

5

Should we use gene drive technologies to control invasive species, and if so, under what circumstances? How can we weigh the moral value of different species, and balance the interests of humans and non-human animals? How can we compare the benefits, risks, and harms of current strategies such as pesticides with those of gene drive technologies? And who should decide on these issues?

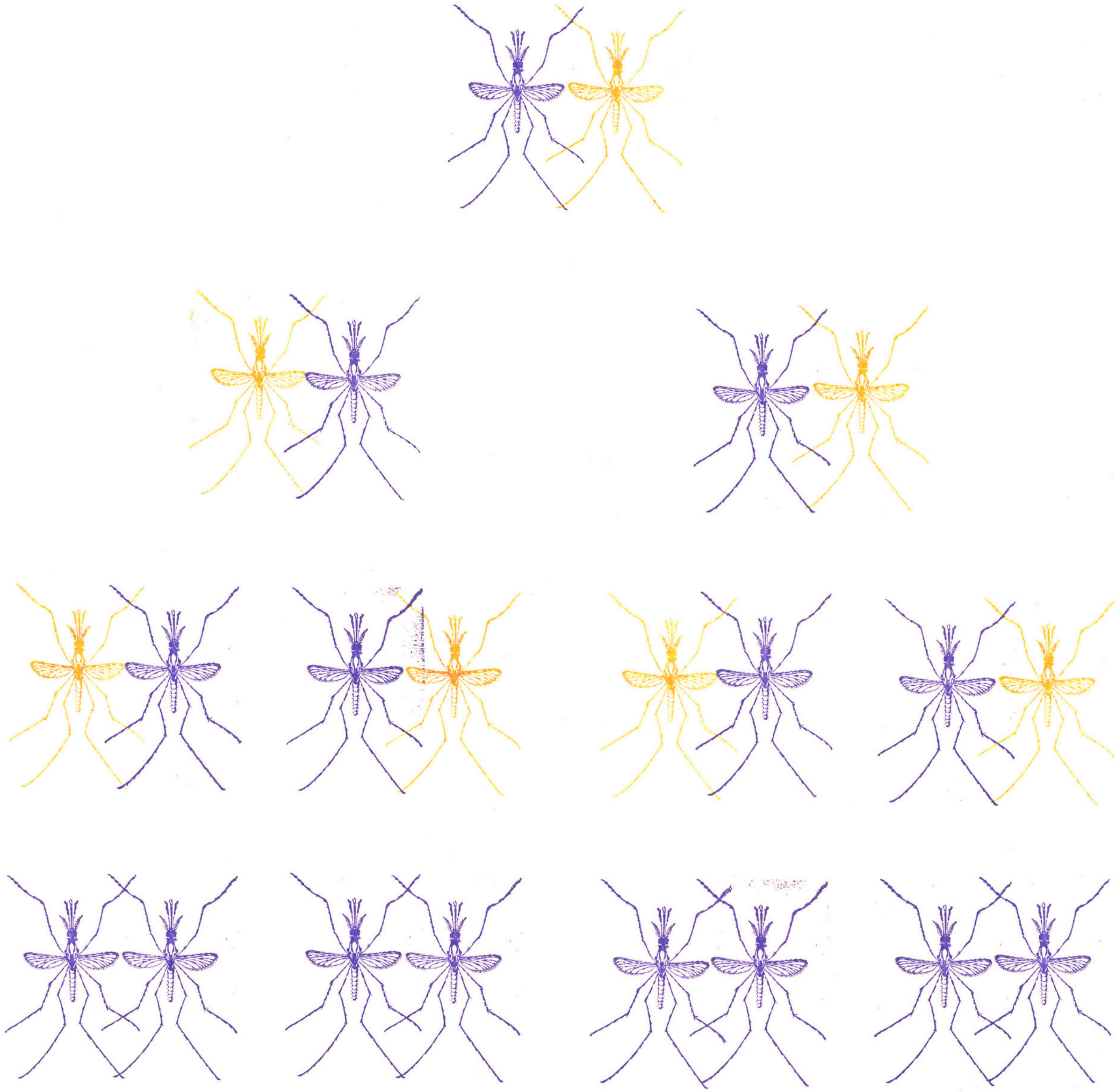





II

ETHICAL LANDSCAPING –
EVALUATING RESPONSIBLE DEVELOPMENT AND GOVERNANCE OF GENE DRIVE TECHNOLOGIES



6

ALLEVIATING THE BURDEN OF MALARIA WITH GENE DRIVE TECHNOLOGIES? A BIOCENTRIC DEFENSE OF THE MORAL PERMISSIBILITY OF MODIFYING OR ERADICATING MALARIA MOSQUITOES

Nienke de Graeff
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Under review

Abstract

Gene drive technologies (GDTs) have been proposed as a potential new way to alleviate the burden of malaria yet have also raised ethical questions regarding the moral permissibility of using these technologies to intentionally eradicate or modify mosquitoes to alleviate the burden of malaria. Engaging with concerns regarding the tendency of humans to consider themselves superior over non-human nature, this paper evaluates whether the inherent worth of individual mosquitoes may provide reason to refrain from using GDTs. First, we outline various perspectives on which organisms matter morally for their own sake, adopting the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes *equal* inherent worth to all life forms. Second, we explore how conflicting claims towards different organisms should be prioritized from this perspective and apply this to the context of malaria control using GDTs. Our ethical analysis shows that this context invokes the principle of self-defense, which overrides the prima facie concerns that a biocentrist would have against the use of GDTs. This leads us to conclude that, as long as certain conditions are met, these considerations do not provide overriding arguments against the deployment of GDTs to alleviate the burden of malaria.

Introduction

Malaria continues to have an enormous negative health impact, claiming the lives of 627.000 individuals and affecting a total of 241 million people in 2020 alone (1). Children, the elderly, and people living in poverty are disproportionally impacted (1,2). Although antimalarial medication and preventive measures such as bed nets and insecticides have led to a decline in morbidity and mortality over the years, further progress is amongst others hindered by drug and insecticide resistance (3). Moreover, even optimal application of existing interventions may not be sufficient to alleviate its burden in highly affected regions (3). The morbidity and mortality of malaria, coupled with the inefficiency of conventional strategies, has provided an incentive to develop innovative strategies to control malaria, such as gene drive technologies (GDTs) (4–7).

GDTs are developed with the aim of promoting the rapid, progressive spread of a particular genetic element within a population of non-human organisms. If organisms reproduce quickly, the genetic element could spread rapidly and permanently across this population (8). The most common vector for malaria in sub-Saharan Africa, and therewith also the primary mosquito species that is studied in the context of applications of GDTs to target malaria[19], is *Anopheles gambiae. Anopheles gambiae sensu stricto* is one of more than 3000 mosquito species that exist globally (9). If GDTs are successful, these technologies could be used for two main strategies of mosquito control. In the first strategy, 'population replacement', the spread of the genetic element changes the genotype of the mosquito species, making them resistant to malaria (10). In the second strategy, 'population suppression', the spread of the genetic element in question causes the number of mosquitoes in a population to decrease, for example by reducing the fertility of a mosquito species or by biasing sex ratios (11).

While the prospect of a potential new way to alleviate the burden of malaria has led to excitement, GDTs have also raised ethical questions regarding the moral permissibility of using these technologies to intentionally eradicate or modify mosquitoes to alleviate the burden of malaria (7,8,12–17). Thus far, ethical analyses of this matter have focused predominantly on whether it is morally justifiable to use a suppression drive to intentionally eradicate a mosquito *species* (7,12,13), with various authors arguing that this can indeed be morally justified. Daniel Callies and Yasha Rohwer analyzed the instrumental and intrinsic value of *Anopheles gambiae.* They argued that this species has redundant instrumental value and no objective 'final' or intrinsic value and that its eradication would correspondingly be morally permissible (12). Similarly, Jonathan Pugh has argued that mosquito species do not hold a significant degree of moral status, and could thus be eradicated (7).

19 While this paper focuses on the application of GDTs in the context of malaria, these technologies have also been proposed as a potential strategy to control other vector-borne diseases, invasive species and agricultural pests (8).

However, next to the value of the species, another key concern in determining the moral permissibility of using GDTs regards the question how the intrinsic value and interests of *individual* humans, non-human animals and the environment should be balanced (8,14,17). While some may consider it evident that human interests trump those of the non-human world, others have argued that beliefs of human superiority over non-human nature should be re-evaluated and that the intrinsic value or inherent worth of non-human organisms should also be taken into account in analyzing the moral permissibility of GDTs (14,18–20). This paper engages with these concerns by evaluating whether the inherent worth of individual mosquitoes may provide reason to refrain from using GDTs. We will argue that *even if* one adopts the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes *equal* inherent worth to all life forms – it can be considered morally permissible to modify or eradicate malaria mosquitoes using GDTs.

Our argument is built up in the following way. First, we outline various perspectives on which organisms matter morally for their own sake, adopting a biocentric perspective. Second, we explore how conflicting claims towards different organisms should be prioritized from this perspective and apply this to the context of malaria control using GDTs. Our ethical analysis shows that this context invokes the principle of self-defense, which overrides the prima facie concerns that a biocentrist would have against the use of GDTs. This leads us to conclude that, as long as certain conditions are met, these considerations do not provide overriding arguments against the deployment of GDTs to alleviate the burden of malaria.

Evaluating which organisms matter morally for their own sake

Which types of organisms should we take directly into account in our decision-making, i.e. which beings matter morally for their own sake? This is a question that has been occupying ethicists for a long time. Roughly categorized, moral status, intrinsic value, or inherent worth[20] may be attributed to humans only (anthropocentric theories), to both humans and animals (zoocentric theories) or to all living organisms (biocentric theories). Whether moral status is attributed to different organisms has implications for our duties towards these organisms, and thereby for evaluating the moral permissibility of deploying GDTs.

The archetypical examples of entities that are considered to matter morally for their own sake are, of course, humans (21). Whilst some theories ground human moral status in membership to the human species, many theories relate it to their possession of particular capacities (e.g. possessing consciousness, being a rational agent or being able to act out of duty or respect for the moral law) or their potential (e.g. to become a rational agent) (22). Some ethical theories ascribe moral status to humans only. According to these theories, humans only have direct duties towards other humans. To the extent that we have obligations towards other entities, these obligations are indirect, i.e. they arise out of obligations to our fellow humans. We may, for example, have a duty to conserve nature, yet for the enjoyment and benefit of (future) humans rather than for nature's own sake (23). Correspondingly, from this perspective it would be morally permissible to deploy GDTs for any purpose, be it alleviating the burden of malaria or anything else – in any way *as long as* it (overall) benefits (future) humans.

Zoocentric theories also ascribe moral status to (some) non-human animals (from here on: animals) and correspondingly consider humans to have direct rather than only indirect duties towards them. From this perspective, both the direct effects on and duties to humans and animals should be considered in the assessment of the moral permissibility of deploying GDTs to target malaria. Different zoocentric theories (e.g. Singer's utilitarian approach (24), Nussbaum's capability approach (25), and Regan's rights-based approach (26,27)) take different characteristics as a basis for moral considerability. Correspondingly, they include different organisms in the moral realm. In his analysis of the moral permissibility of eradicating mosquitoes with GDTs, Pugh adopts Singer's consequentialist zoocentric perspective, in which sentience is a necessary condition to afford organisms moral status (24). Since it is not clear that mosquitoes possess sentience, he argues, it is not clear that they should be attributed moral status (7). Correspondingly, he contends that neither individual mosquitoes nor the species as a whole possess moral status and that these considerations thus do not provide an argument against eradicating mosquitoes with GDTs.

However, what if all living organisms are considered to have moral status or inherent worth? Biocentric theories attribute all living beings the same inherent worth; the only ground to attribute inherent worth to is considered to be life itself (28). This perspective thus aligns well with the position of those that have argued that the moral worth of non-human organisms should also be taken into account in the evaluation of the moral permissibility of GDTs and that beliefs of human superiority over nature should be re-evaluated (14,18–20). An important biocentric theory is the theory of Paul Taylor (29,30), who argues we ought to adopt a 'biocentric outlook'. This refers to a species impartial view which is amongst others grounded in the recognition that all individual organisms are "*teleological centers of life in the sense that each is a unified, coherently ordered system of goal-oriented activities that has a constant tendency to protect and maintain the organism's existence*" (p. 122) (30). While Taylor acknowledges that humans, as moral agents, have capacities such as rationality that other organisms lack,

20 Notably, there has been substantial discussion about what these concepts mean and the need to distinguish these concepts from each other, see e.g. (27,29,40,41). While we acknowledge this, a thorough discussion of these matters is beyond the scope of this paper. Where relevant, we will specifically refer to the term used by the authors upon whose work we reflect.

he denies this makes us superior to them. This biocentric outlook, in turn, warrants the adoption of a moral attitude of 'respect for nature' (p. 86) (29), which undergirds the acceptance of a system of basic rules of conduct. Amongst others, these rules include the 'rule of noninterference' that holds that we should allow other organisms to fulfill their own desires and adopt a hands-off policy. Based on this rule, and in line with the argument that the use of GDTs would be contrary to a principle of noninterference (18), the use of GDTs may be considered prima facie morally impermissible from a biocentric perspective.

Be that as it may, one may question whether a biocentric perspective is morally tenable in the first place, as has been done in the literature on GDTs as well as environmental ethics more generally. In a discussion of the interrelationship between the moral status of species and the moral status of individual mosquitoes, Pugh for instance contends that views that attribute moral status to all living things or species have indefensible conclusions that would amount to a *reductio ad absurdum* that opponents of GDTs cannot plausibly defend (7). To avoid the conclusion that some of modern medicine's greatest triumphs such as the eradication of the variola virus are morally impermissible, he argues, opponents of GDTs must provide an argument as to why we have reason not to eradicate mosquito species that do not apply to viruses and other life forms. To do so, he contends they "*must appeal to a more nuanced picture whereby not all living things (..) have moral status*" (p. 579) (7). Similarly, other philosophers have provided critiques of biocentrism, for instance questioning whether all different organisms in fact command equal respect and whether being a teleological center of life can be considered morally significant at all (31–34).

For the purposes of this paper, however, it is not necessary to evaluate these arguments and provide a defense or rebuttal of biocentrism. Surprisingly, it can be considered morally permissible to modify or eradicate malaria mosquitoes using GDTs *even if* we, for the sake of argument, adopt the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes equal inherent worth to all life forms. To substantiate this claim, the next section explores how Taylor's biocentric theory approaches conflicting duties to different organisms.

Prioritizing conflicting duties to different organisms

To determine the moral permissibility of GDTs from a biocentric perspective, it is essential to investigate how this perspective prioritizes conflicting duties to different organisms. As was mentioned in the previous section, Taylor's biocentric theory attributes the same inherent worth to all living organisms. Correspondingly, he argues we have duties towards all living organisms, including mosquitoes.

Simultaneously, Taylor argues that the attitude of respect for nature should continue to be accompanied with that of respect for persons, acknowledging that this will inevitably lead to fundamental moral dilemmas. After all, many activities that advance human interests or fulfill human rights conflict with the good of non-human organisms (29). While duties towards (other) humans should not automatically be given greater weight than our duties to non-human organisms, humans – as moral agents[21] – are permitted to let their interests take precedence over those of non-human organisms in specific situations. For cases where a fundamental moral dilemma exists due to a conflict between the realization of human values and the good of other living organisms, Taylor stipulates five principles to resolve and prioritize conflicting claims. The first of these five principles, the principle of self-defense, applies when wild organisms are harmful to humans, i.e. when these organisms threaten humans *basic interests* such as survival or health[22] (30). Specifically, the principle of self-defense states that it is "*permissible for moral agents to protect themselves against dangerous or harmful organisms by destroying them*" (p. 264-5) (30). Like we may, if need be, forcefully protect ourselves from an attacking human that threatens our life, this also holds if we are threatened by non-human organisms. Upholding or carrying out such a principle does not imply that an attacking or threatening organism (be they human or non-human) has a lower inherent worth than the organism that engages in self-defense, nor that it is morally permissible to use force upon them or use them to further our interests in other contexts.

In this context, Taylor defines self-defense as "*defense against harmful and dangerous organisms*", and a harmful or dangerous organism is taken to be "*one whose activities threaten the life or basic health of those entities which need normally functionally bodies to exist as moral agents*" (p. 265) (30). As we saw in the introduction, the transmission of malaria from mosquitoes to humans most definitely threatens humans' lives and basic health: it killed 627.000 individuals and affected a total of 241 million people in 2020 alone (1). Indeed, it has been claimed that *Anopheles gambiae* is the "*deadliest animal in the world*" (p. 194) (12). Correspondingly, these mosquitoes certainly meet the definition of 'harmful and dangerous organisms' and the principle of self-defense indeed seems to apply. If this is so, the principle of self-defense would override the prima facie duties towards mosquitoes and could justify "*destroying them*" (p. 264-5) (30). At the same time, Taylor contends that the principle of self-defense only holds if several conditions are met. The next section evaluates whether these conditions can be met in the context of using GDTs to alleviate the burden of malaria and addresses possible objections to our argument.

21 Moral agents, as beings who can reflect on how they act, are the only beings who can reasonably be ascribed duties, obligations and responsibilities that are owed to them. Taylor argues that if there turn out to be non-human moral agents whose existence is threatened by humans, it would equally be morally permissible for those non-human moral agents to kill those humans (29).

22 The other four priority principles, which are not discussed in this paper, apply to situations where the *non-basic* interests of humans – i.e. those interests that we have based on our individual value systems rather than based on universal values or primary goods that make up our basic interests – are in conflict with the (basic or non-basic) interests of non-human organisms (30).

The principle of self-defense in context: morally evaluating the use of GDTs

According to Taylor, the principle of self-defense holds only when two conditions are met. The first condition holds that "*moral agents, using reasonable care, cannot avoid being exposed to such organisms and cannot prevent them from doing serious damage*" (p. 265) (30). Whether this condition can be met in the context of using GDTs hinges on what we take 'reasonable care' to mean. This concept is often defined as "*that care which a person of ordinary prudence would use in order to avoid injury to themselves or others under circumstances similar to those shown by the evidence*" (p. 72) (35). In the case under analysis, of course, we cannot assess this for all malaria patients individually, but on a collective level, it is clear that major investments have been made in preventive measures such as bed nets and therapeutic measures such as malaria medication (1,3). At the same time, it may be argued that humans have failed to invest sufficiently in improvements to the global health system, which undergirds the problem of malaria (14). Indeed, there is a strong relationship between the availability of health care facilities, socioeconomic status, and the removal of stagnant water on the one hand, and the morbidity and mortality of malaria on the other. If more was invested to improve the social determinants of health, the impediments of vector-borne diseases could be lowered (36,37). However, while this points towards an important concomitant duty to invest (more) in such measures, it would be a stretch to argue that fundamentally changing the prevailing health care and sociopolitical systems in malaria-endemic countries would be an act of 'ordinary prudence'. With the enormous amounts of money, time and energy spent on strategies to prevent mosquitoes from spreading malaria in the past decades (1,3) it can overall be concluded that while humans have succeeded in reducing the exposure to and negative impact of malaria mosquitoes using reasonable care, they cannot avoid being exposed to such organisms nor prevent them from threatening human health and survival. In principle, this confirms the applicability of the principle of self-defense and could provide a justification to "*destroy*" malaria mosquitoes (p. 264-5) (30).

However, does this also justify the use of GDTs? This is where Taylor's second condition comes into play. The principle of self-defense can only be justified if "*only those means are used that will do the least possible harm to the organisms consistent with the purpose of preserving the existence and functioning of moral agents. There must be no available alternative that is known to be equally effective but to cause less harm to the 'attacking' organism*" (p. 265) (30). The moral permissibility of using GDTs, in other words, depends on how effective and harmful these technologies are in comparison to other available alternatives. When it comes to alleviating the burden of malaria, various alternatives are currently available, including bed nets, insecticides, malaria vaccines and the destruction of vector habitats (9). As has been clear from

the discussion thus far, these alternatives have not been successful in sufficiently alleviating the burden of malaria. Although malaria vaccines have shown promise, it is unlikely that a long-term efficacious vaccine will be available soon (38,39). Moreover, many of the currently used alternatives cause more harm to the 'attacking' organism than a GDT would be likely to cause. One of the most prominent strategies that is currently used to alleviate the burden of malaria – insecticides – kills malaria mosquitoes, whereas GDTs would genetically modify them to either become resistant to the malaria parasite, reduce their fertility, or only get male offspring. At best, a GDT would not harm the mosquito in any way, and at worst (e.g. if it reduced a mosquito's fertility and thereby disrupted one of its goal-oriented activities directed towards its preservation, or if the GDT had off-target effects that were harmful to it) it would do less harm to the individual organisms than insecticides that kill mosquitoes. If this is so, then a biocentrist would indeed have reason to support the use of GDTs (and in fact, to prefer it to other alternatives) so that humans could defend themselves from being harmed by malaria mosquitoes.

Nevertheless, it may be questioned if these considerations could justify both the use of a replacement drive that would modify a mosquito population as well as a suppression drive that would (at least in theory) eradicate it. Indeed, Taylor considers it prima facie morally impermissible to eradicate a species-population, yet not for the sake of the population as a whole. While he considers it statistically intelligible to speak of furthering the good (and vice versa, decreasing the good) of a whole species-population, he does not consider the population as such to have a good of its own that is independent of the good of its individual members (30). That being said, eradicating a species-population of mosquitoes through a suppression drive could still be considered harmful to a species-population from a biocentric perspective as it would lower the "*median level of their good-realization*" (p. 69) (30). Whether this is morally acceptable, in turn, would again depend on the available alternatives. If, for instance, there was a choice between an effective replacement drive and an effective suppression drive, a replacement drive could be considered preferable since it would cause less harm to the mosquitoes than the suppression drive. If no effective replacement drive was available, however, the biocentrist's prima facie objections against using a suppression drive would be overridden given the applicability of the principle of self-defense.

Finally, it could be objected that while the principle of self-defense might be applicable to those individual *Anopheles gambiae* mosquitoes that could in fact harm us, i.e. that *actually* carry malaria, it would not apply to other individual *Anopheles gambiae* mosquitoes that do not carry the malaria parasite. Indeed, the principle of self-defense does not justify harming organisms that do not harm us. At the same time, Taylor stipulates that it can nonetheless be permitted to harm creatures that do not harm if doing so "*is a practical necessity arising from a situation where we cannot* *separate harmless organisms from the harmful ones against which we are defending ourselves*" (p. 266) (30). In the context of malaria, this is indeed the case: thus far, we have not found a way to specifically target malaria-carrying mosquitoes, and our other alternative methods such as insecticides similarly target *all Anopheles gambiae* mosquitoes[23] rather than only the malaria-carrying mosquitoes.

Concluding remarks

All in all, our analysis demonstrates that Taylor's principle of self-defense is applicable to the situation of using GDTs to alleviate the burden of malaria. This leads us to conclude that even if one adopts the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes equal inherent worth to all life forms – it is prima facie morally permissible to modify or eradicate malaria mosquitoes using GDTs. Of course, this is but one of the ethical considerations that are relevant to determine the 'all things considered' moral permissibility of doing so, and important other considerations will include assessing the potential negative effects on other organisms. Moreover, as this paper underlines, *if* GDTs are deployed, the approach to tackling malaria should remain multifaceted and interventions that address underlying health and socioeconomic problems, in particular, should be maintained and/or intensified alongside GDTs.

6

23 More generally, insecticides cause a lot of 'collateral damage' as they also harm other mosquitoes and organisms. As GDTs are intended to specifically target one species of mosquitoes (9), their 'collateral damage' could be expected to be lower.

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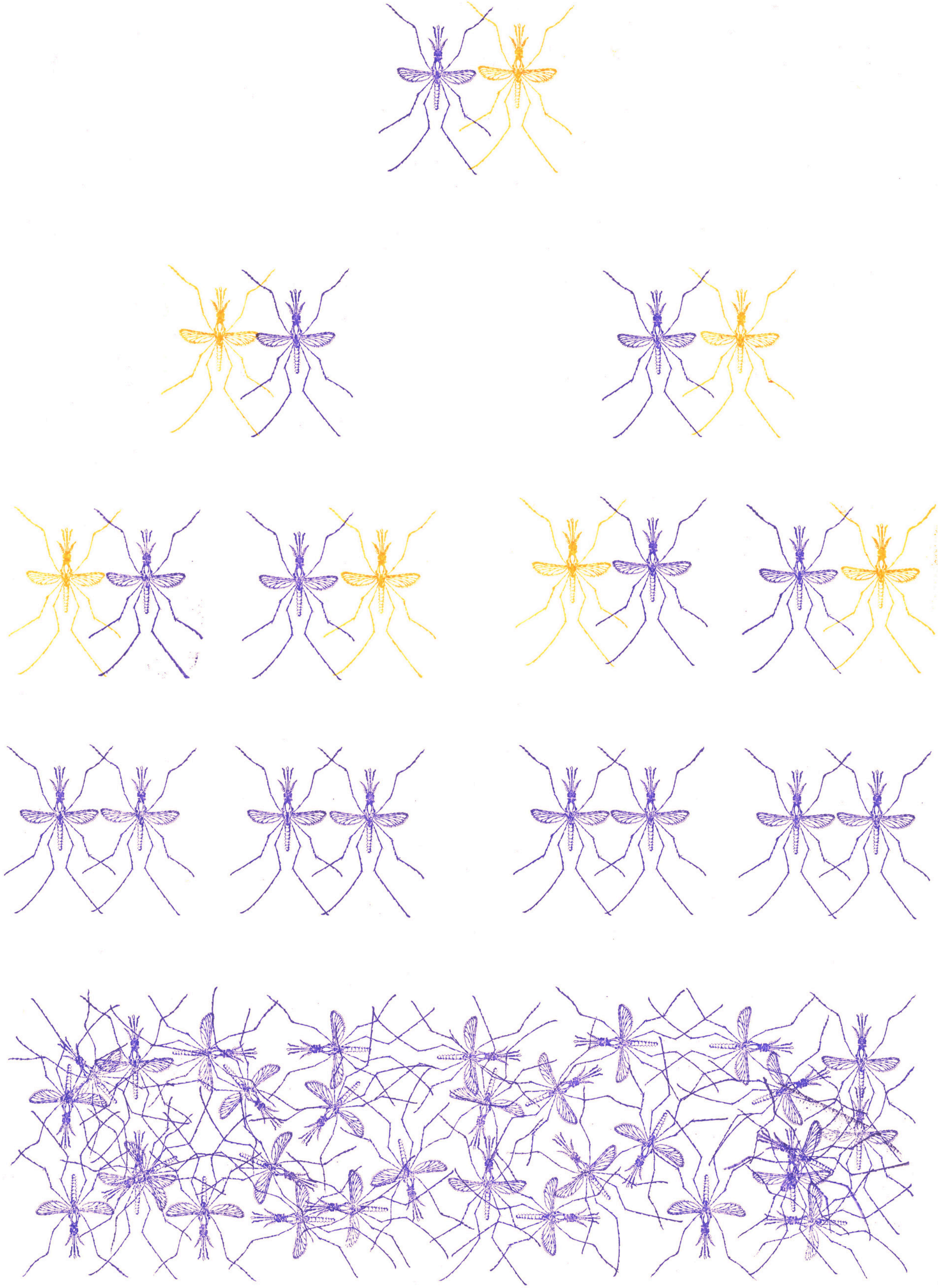

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FAIR GOVERNANCE OF BIOTECHNOLOGY: PATENTS, PRIVATE GOVERNANCE AND PROCEDURAL JUSTICE

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Patents and private governance

In their article "Patenting Foundational Technologies: Lessons From CRISPR and Other Core Biotechnologies," Feeney and colleagues (1) provide a critical analysis of Farrelly's take on patents (2). Patents serve to encourage investments needed to get new biotechnologies on the market, yet may also raise distributive justice concerns by delaying development and limiting access to the patented technology, as Feeney and colleagues (1) point out. Such inequality in access is particularly problematic for what they refer to as "foundational" technologies, given their great promise for both fundamental research and therapeutic applications. To mitigate these concerns, a number of ways are suggested to curtail the exclusivity afforded by patents on foundational technologies so as to increase access to these technologies. In doing so, the authors adopt a nonideal perspective toward patents, taking a real-world starting point.

As Feeney and colleagues (1) discuss, patents are "rights of exclusivity" and can thus also be employed to achieve private governance. Private governance occurs when certain phenomena, such as the use of new biotechnologies, are regulated by private agents rather than through governmental policies. Correspondingly, exclusive rights can give patentees the power to direct others' use and research for private good, but also for societal good through so-called "ethical licensing" (3). The license that Editas Medicine, Inc. (Editas), the surrogate licensee to which the Broad Institute has outsourced its licensing and commercialization rights, granted to Monsanto (recently acquired by Bayer) is an example of such ethical licensing. In this license, specific applications were expressly prohibited, such as the creation of sterile "terminator" seeds or the conduct of research aimed at commercializing tobacco products (1). Similarly, Kevin Esvelt proposed using gene drive patents to prevent others from using this technology without disclosing their research plans and accompanying safety and ethical issues (4,5).

While we are sympathetic to the nonideal perspective adopted by Feeney and colleagues (1) and agree that it is important to address the distributive justice concerns of biotechnology patents, their approach fails to address concerns of procedural justice raised by the use of exclusivity rights for private governance. Like Feeney and colleagues (1), we consider it praiseworthy that patentees such as Editas aim to pursue a socially responsible approach in their licensing agreements, but we argue that using property rights in this way raises concerns beyond the mere issue with the voluntariness of adopting a socially responsible approach that they bring forward. In what follows, we discuss why this is the case, why procedural justice matters, and propose a potential solution to mitigate these concerns.

Private governance and procedural justice

Foundational technologies such as CRISPR (clustered regularly interspaced palindromic repeats) are exceptional not only in terms of the promises they hold for fundamental research and therapeutic applications, but also in terms of the discussion and disagreement they generate about what would constitute "socially responsible" or "ethical" use of these technologies. As there is no widely accepted, independent criterion to determine this, such value pluralism poses a legitimacy problem: who should be allowed to decide this, and under what conditions?

By leaving the determination of what is "socially responsible" or "ethical" to the sole discretion of the patentee, ethical licensing through private governance raises not just distributive justice concerns, but also concerns related to the fairness of this decision-making process: concerns of procedural justice. Given the absence of a widely accepted criterion to determine what counts as a "socially responsible" or "ethical" application of new foundational technologies, ethical licensing should foster broad debate about whether and when these epithets apply, rather than leaving it solely up to the patentee to determine this.

We contend that the societal importance of foundational biotechnologies provides a rationale not only to impose obligations on patentees to increase access to these technologies, but also to safeguard the fairness of regulatory processes for the use of these technologies. A fair process can provide a legitimization for the way in which decisions about the use of these technologies are made (6), even though it has been argued that a fair process does not guarantee that the resulting outcome is just.

Although it is beyond the scope of this commentary to specify necessary and sufficient conditions to achieve procedural justice in ethical licensing, such a process should at a minimum allow a broader group of stakeholders, other than just the patentee, to have insight and influence in those terms of the license that govern acceptable uses of the technology. Furthermore, the debate about these restrictions should be made as transparent as possible, allowing the community at large to hold patentees and licensees accountable for the arrangements made.

Addressing the procedural justice concerns in ethical licensing

In the field of genome editing broadly construed, the need for stakeholder engagement in the discussion about the governance, applications and use of these technologies is widely acknowledged. Among others, Jasanoff and Hurlbut (7) have proposed a "global observatory," an international network of different stakeholders that should deepen and enrich the debate about biotechnologies. Similarly, patent scholars have come up with proposals to increase responsiveness to societal interests. Howe (8), for example, has defended a community-oriented concept of patents that entails obligations for patentees on green technologies to contribute to a better environment, the so-called “stewardship” model.

We acknowledge that different strategies may be employed to increase procedural justice in ethical licensing. One solution might be to allow democratically chosen governments to control or oversee licensing conditions. Given their democratic legitimacy, such governmental involvement could increase procedural justice. Nevertheless, we believe this solution poses two problems. First, this approach would strongly compromise the rights of patentees and thereby threaten the further development of these technologies in the first place, raising distributive justice concerns as patentees would be less likely to invest in new technologies. Second, it would result in internationally fragmented policies, as different governments will likely come to different regulatory frameworks. A second solution, advanced here, circumvents these problems by acknowledging that patents incentivize research investments in biotechnologies (2). At the same time, this solution diminishes problematic characteristics of private governance by allowing other stakeholders to have insight and influence in decision making about acceptable use of these technologies, thereby optimizing the balance between procedural justice and distributive justice.

Specifically, we suggest creating a platform akin to the Creative Commons platform in the creative industry. Creative Commons unites different stakeholders from the creative industry to formulate a model license, reflecting what the stakeholders agreed is a fair balance between the rights of creators and the public. Although the use of a Creative Commons license is not mandatory and may be tailored to the wishes of the copyright holder, it has set a “gold standard” for open licensing of creative content. Adherence to this gold standard can have important reputational benefits for copyright holders, in addition to encouraging widespread dissemination of their work.

A similar process could be facilitated by a platform that brings together stakeholders from the CRISPR community, including scientists, research institutes, patient organizations, and pharmaceutical companies, such as the one proposed by Jasanoff and Hurlbut (7). Even in the absence of full agreement on the ethical use of a technology such as CRISPR, these stakeholders could jointly formulate a guideline in which consensus is specified. As mentioned previously, this platform should be open to the public to the extent possible to allow public scrutiny of (debates on) the contents of the guideline. The best practices thus formulated could become a guideline for ethical use of the technology in question and a model license for those wishing to license the technology.

Of course, the voluntariness of committing to such a platform’s blueprint license poses problems. These problems might be alleviated by making government grants conditional on the recipient’s commitment to the platform’s principles, among other

solutions. Moreover, the shift toward more openness and societally responsible use of intellectual property that has been observed over the past years in various industries, such as the publishing industry, stems hopeful. Within the CRISPR community, the example of Editas shows that also in this industry, patentees are receptive to societal interests and appear willing to take them into account in the execution of their rights.

Concluding remarks

By leaving the determination of “socially responsible” use of foundational technologies to the sole discretion of the patentee, ethical licensing through private governance raises concerns of procedural justice. It is imperative to urge the pursuit of policies that encourage broader insight and influence in this process, such as the one advanced here, to ensure legitimate decision making on technologies that have broad societal impact.

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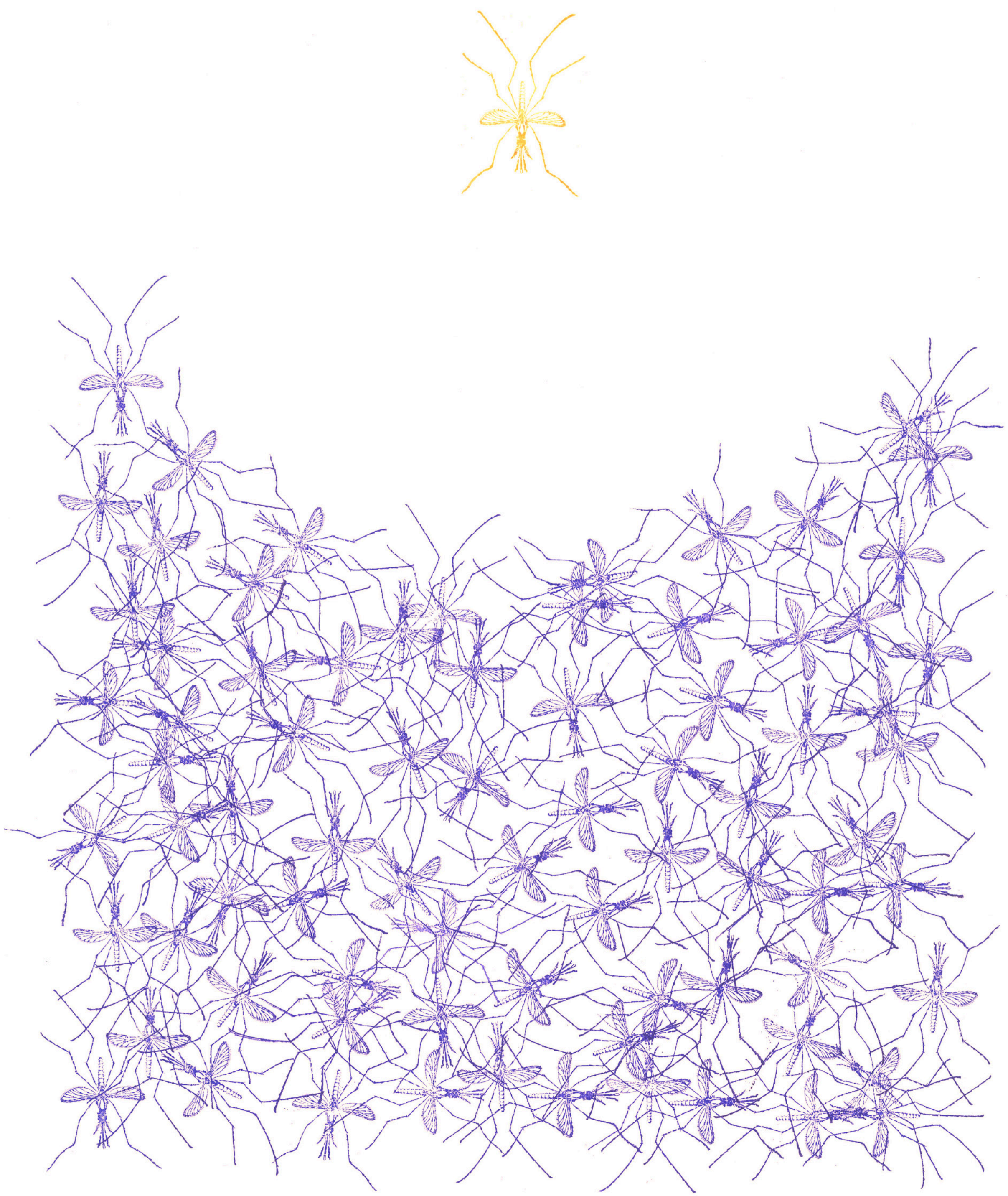

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THE BOUNDARY PROBLEM: DEFINING AND DELINEATING THE COMMUNITY IN FIELD TRIALS WITH GENE DRIVE ORGANISMS

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Under review

Abstract

Despite widespread and worldwide efforts to eradicate vector-borne diseases such as malaria, these diseases continue to have an enormous negative impact on public health. For this reason, scientists are working on novel control strategies, such as gene drive technologies (GDTs). As GDT research advances, researchers are contemplating the potential next step of conducting field trials. An important point of discussion regarding these field trials relates to who should be informed, consulted, and involved in decision-making about their design and launch. It is generally argued that community members in particular have a strong claim to be engaged, yet disagreement and unclarity exist about how this 'community' should be defined and delineated. In this paper, we shed more light on this 'boundary problem': the problem of determining how boundaries of in- and exclusion in (GDT) community engagement should be drawn. As our analysis demonstrates, the process of defining and delineating a community is itself normative. First, we explicate why it is important to define and delineate the community. Second, we demonstrate that different definitions of community are used and intermingled in the debate on GDTs, and argue in favor of distinguishing geographical, affected, cultural, and political communities. Finally, we propose initial guidance for deciding who should (not) be engaged in decision-making about GDT field trials, by arguing that the definition and delineation of the community should depend on the rationale for engagement and that the characteristics of the community itself can guide the effective design of community engagement strategies.

Introduction

Despite widespread efforts to eradicate vector-borne diseases such as malaria, these diseases continue to have an enormous negative impact on public health. In 2020, malaria alone affected 241 million individuals (1). While antimalarial medication and preventive measures such as bed nets and insecticides have led to a decline in malaria deaths from 896.000 in 2000 to 627.000 in 2020, further progress in preventing malaria is hampered by a lack of financing and the emergence of drug and insecticide resistance (1,2). Moreover, even optimal application of these interventions may not be sufficient to eliminate the disease in highly affected regions (2).

For these reasons, scientists are working on novel vector control strategies, such as gene drive technologies (GDTs). GDTs promote the biased inheritance of certain genetic elements from generation to generation (3), thereby fostering their rapid spread across a population of non-human organisms. In the context of malaria, GDTs could be used to reduce mosquitoes' capacity to spread malaria or their capacity to reproduce (4). As GDT research in laboratory and confined cage studies advances, researchers are contemplating the potential next step of conducting field trials to assess their performance in real-world conditions (5). This has led to significant debate about whether, and if so, under what conditions these potential field trials should be carried out (5–8).

One point of discussion regarding these potential field trials relates to who should be involved in the deliberation and decision-making about them. It is generally argued that the interests of a wide range of stakeholders should be considered, but that community members in particular have a strong claim to be informed, consulted and involved in decision-making about the design and launch of potential GDT field trials (9–12). Amongst others, rationales for community engagement include instrumental considerations such as that community involvement could lead to better (informed) decisions, could prevent resistance from the community or could enhance trust in gene drive research; considerations of procedural justice since community members' health and environment could be impacted; and considerations of restorative justice in the context of past harm or historical injustices in decision-making procedures in particular research settings (7,9,13–16).

Despite broad consensus about the importance of community engagement, however, a challenge remains with regard to whom the 'community' refers: the concept is often ill-defined or understood in different ways (14,17–19).[24] David Hunter and Jacob Leveridge, for instance, note there are "*different understandings of who or what constitutes a 'community" (..) [yet] the concept is often picked up and used*

24 The meaning of 'engagement', 'involvement' and 'participation' poses an additional challenge (22,68,69). While an analysis of these notions is not the focus of this paper, we will argue that a further conceptualization of 'community' can also help to determine how engagement should be operationalized.

with little reflection on its philosophical underpinnings" (p. 12) (17). It has even been argued that the term community is an 'empty signifier' that is "*deployed to signal a commitment to local perspectives, but often not carried out in a meaningful way"* (p. 259) (20).

The challenge of defining and delineating the community is also recognized in the literature on GDTs. The foundational report on GDTs that was written by the National Academies of Sciences, Engineering and Medicine (NASEM), for instance, contends that determining how boundaries of in- and exclusion in community engagement should be drawn is one of the key challenges related to GDTs (13). Various other authors consider defining and delineating communities to be of central importance to responsible gene drive research and vital to designing an effective deliberation framework and decision-making strategy (10,11,18).

In this paper, we shed more light on this 'boundary problem' – how boundaries of in- and exclusion in community engagement should be drawn – in the context of GDTs.[25] First, we elaborate on why it is important to define and delineate the 'community' in this context. Second, we demonstrate that different definitions of community are used and intermingled in the debate on GDTs, highlight complexities with further delineating who are a part of the community, and argue in favor of distinguishing geographical, affected, cultural, and political communities. Finally, we propose initial guidance for deciding who should be involved in decision-making about GDT field trials, by arguing that the definition and delineation of the community should depend on the rationale for engagement. Moreover, we demonstrate that the characteristics of the community itself can guide the effective design of community engagement strategies.

Why is it important to define and delineate the community?

There are several reasons why it is important to define and delineate whom the community comprises.

First and overarchingly, a definition and delineation of the community is necessary for the design of effective and just community interventions (19,21–24). As the introduction highlighted, the concept of community is often tied to particular obligations towards its members in the context of global health research generally, and GDT research specifically. Defining and delineating the community is therefore not just a conceptual, but also a normative process: it is necessary to pinpoint to *whom* these obligations exist (14,17,25). If the wrong people are engaged and/or

25 This problem is also relevant to community engagement in the context of other research. More broadly, there is also a 'boundary problem' in democratic theory (70).

people are overseen in engagement efforts, this could threaten the procedural justice and legitimacy of the resulting decisions.

Second, a lack of a definition and delineation of the community can create obstacles in determining who can adequately represent a community in an engagement process (10,21,22) and undermine the ability to evaluate community engagement efforts (21,22). The representation of a community could be determined based on whether particular individuals share particular characteristics with the larger community and/or whether they possess the legitimate political authority to represent it (26), which can only be determined once the community itself has been defined and delineated. Similarly, if it is unclear where the boundaries for in- and exclusion of community engagement should be drawn, it is impossible to evaluate whether particular projects or procedures succeeded in engaging the intended people. A clear definition and delineation of the community is also necessary for the institutional ethics committee that must evaluate and approve the proposed community engagement process (27).

Third, a lack of a definition and delineation of the community can lead to dissatisfaction, loss of trust, and conflicts between different parties who thought they came to an agreement about the ethical obligations towards communities, yet who actually had diverging and potentially incompatible convictions about where the boundaries of a community should be drawn. If the community is not explicitly defined and delineated, this concept may become so vague or slippery as to mean anything one desires. This vagueness can create hurdles or even obstruct realizing the benefits of a participatory approach (21). It has even been argued that the lack of definition and delineation of the community underlies "*many of the failed expectation*s" around community engagement (p. 3) (22). Diverging assumptions of different parties may not be obvious unless the community is explicitly defined and delineated (21,22). This is particularly relevant in the context of international collaborative research such as GDT research, in which communities are oftentimes defined externally by researchers(14,23), even though 'internal' and 'external' definitions of community may differ (23). The process of defining a community is thus often related to the perspectives of the 'boundary-drawer': the person or group of people who determines who the community is or whom it consists of (14). By explicitly defining and delineating whom the community comprises, both community members themselves and other parties can engage in a discussion about the choices that are made in doing so. This way, other perspectives can be incorporated, failed expectations may be prevented, and the realization of the benefits of a participatory approach are facilitated (7).

For these reasons, it is important to define and delineate what or whom it is we refer to with the term 'community' in the context of GDT development and deployment. Obtaining clarity about this is an essential step in designing meaningful guidelines for the engagement of communities in research (24). In what follows, we first map how the term is used in the GM (genetic modification) and GDT literature and link this use to different definitions and characteristics of community that have been put forward in the community engagement literature.

How is the community defined in the literature on GM and GDTs?

In the literature on GM and GDTs, the term community is used abundantly. In many cases, the term itself is used without being explicitly defined or implicitly described (see e.g. (15,28–31)). In other cases, it is defined explicitly or particular characteristics of a community are underlined. Amongst these different uses, different definitions of community can be identified, namely geographical, affected, cultural and political communities. As is discussed in what follows, each of these definitions of communities has its own characteristics and complexities.[26]

Geographical communities

Many references to the community position communities as groups of people that live in the same geographical locality (22,23,32). The GDT literature frequently refers to such 'geographical communities', for instance when it is argued or implied that "*local communities*" should be engaged (4,33–39), when communities are defined as the groups "*in the immediate vicinity of field trials*" (p. 1096) (40) and when it is stated that community engagement is mainly focused on "*communities around the insectary*" where research is conducted (p. 4) (41). In an expert workshop organized by Target Malaria, the Kenya Medical Research Institute (KEMRI) and the Pan African Mosquito Control Association (PAMCA), geographic location was also considered essential to determine whom to engage and how (10).

This short analysis already underlines some characteristics of geographical communities and complexities related to this definition. On the one hand, geographical borders are generally clearly delineated, such that boundaries of in- and exclusion could be well-defined once the appropriate geographical locality for engagement is determined. Additionally, geographical communities often share decision-making structures that could be used to give them a voice in providing input on a decision about a GDT field trial (32). On the other hand, genetically modified organisms (GMOs) are likely to spread beyond pre-defined geographical areas. Additionally, references to these geographical communities for the most part do not specify how the scope of the relevant locality should be determined. Some link the scope of engagement to the people that live in the area where gene drives are released (10,41,42), whereas others

26 These definitions are not necessarily mutually exclusive: some groups of people fit various definitions of 'community', and various authors (implicitly) use multiple definitions.

link it to the areas where GMOs may fly (11). Moreover, what individuals take to be their geographical community can also differ from person to person, and people in the same locality do not necessarily share the same goals or interests (23).

Affected communities

Various references to the community take the relevant community to constitute a group of people whose interests could be affected by the release of GMOs (9,18,50,33,43–49). These (potentially) 'affected communities' are also frequently, but not always, connected to geographical localities. The NASEM, for instance, links geographical and affected communities by defining communities as "*groups of people who live near enough to a potential field trial or release site that they have a tangible and immediate interest in the project*" (p. 131) (13).

This definition of community also provides a justification to engage the community: for reasons of justice, the most affected individuals deserve a strong voice in the decision-making process (9,13,48,51). At the same time, it raises the question when someone is sufficiently 'affected' to be a part of this community. In the NASEM report as well as other references to affected communities, it mostly remains unclear when someone should be considered (potentially) affected in a way that demands their engagement (7). In some cases, further consideration is given to this issue, with different authors providing different perspectives. According to one of the first frameworks for community engagement in the context of field trials with GMOs, a community is defined as "*at least those individuals who share identified risks associated with the proposed research project*" (p. 280) (50). While this definition has a narrow focus on risks, which are not further defined, other definitions such as the NASEM definition focus on "*tangible and immediate interests*" more broadly (p. 131) (13). As Carolyn Neuhaus observes rightly, "*how one defines 'interests' matters when predicting who is affected by field trials and to what extent*" (p. 33) (48). She argues in favor of a broad conception of interest, which includes not only health and safety, but also ways of conceptualizing their relationship to nature (48).

Some authors contend that it matters whether one's interests are 'directly' impacted or not (10,18). David Resnik, for instance, restricts the definition of a community to those people who "*live near enough to the proposed field trial site that their health or environment is likely to be* <u>*directly and immediately*</u> *impacted by the release. This definition would include people living in the area near the field trial site and possibly people living in neighboring areas, depending on how well the release can be contained*" (p. 242, emphasis added) (18). Delphine Thizy and colleagues, in turn, distinguish between communities living in release sites that would be 'directly' affected and communities living in areas where gene drive mosquitoes could spread that would be 'indirectly' affected (10). In their view, all communities would have to be informed and consulted, while only 'directly' impacted communities would have to provide agreement to field trials.

As these examples underline, affected communities are defined in different ways. Moreover, it generally remains unclear how one could distinguish between 'directly' and 'indirectly' affected communities.[27] This vagueness and these differences are all the more pressing given that GDTs are designed to spread, which means that non-localized drives in particular may potentially spread across large areas and could affect many individuals and groups (52).

Cultural communities

Some references to the community (also) refer to communities as groups of people that share certain cultural norms, values and/or traditions (9,10,42,53,54). The World Health Organization, for instance, states that *"community values and concerns are taken into account in research plans at all stages"* (p. 87) (53). Similarly the World Health Organization (WHO) states that it is critical that *"procedures for identifying leaders and representatives, or for interacting with community groups, are based on detailed knowledge of the locale, its traditions, and its history of cooperation, exploitation and conflict resolution"* (p. 96) (53). In these cases, it is stressed that community members may share certain preferences based on their common history and heritage.

If a group of people is a cultural community, the mutual interests they share may help to identify particular individuals as 'representative' of the interests of a community. At the same time, it may be difficult to determine what the defining features of a particular cultural community are, and thereby to determine whether and when one could serve as a representative of the interests of a community. Additionally, the interests of community members may still vary even if they have common values, concerns and interests that define them as a cultural community. Moreover, cultural communities may not be organized in ways that would allow them to reach consensus about the potential benefits of research (55). Finally, GMOs may spread in areas that encompass different communities that may not share mutual interests or culture, which could "*strain the (..) ability of researchers to utilize a similar or generic approach for engagement with different groups*" (p. 8) (10).

Political communities

A few references to the community refer to communities as 'political communities': neighborhoods, townships or social groups in a specific locale that share a governing body (9,53). In its guidance framework, the WHO for instance contends that "*community authorization is a procedure intended to elicit agreement on behalf of a group, often a political community, such as a neighbourhood or township, or social group in a specific locale that shares government"* (p. 96) (53). Resnik similarly assumes

27 In some sense, one could argue that only the mosquitoes themselves are directly affected.

the community is also political community[28] that "*has a legitimate political process for making decisions"* (p. 138) (9).

As these brief reflections imply, the existence of a political community could facilitate the legitimacy of decision-making about GDT research. At the same time, of course, GMOs are not limited by political boundaries (56), just like they are not limited by geographical or cultural boundaries. Moreover, fair procedures do not guarantee substantive fairness. Minorities can, for example, in fact be disadvantaged in liberal representation (9,57).

Bridging types of communities and guidance for engagement

As the previous section demonstrated, the term community is used in different ways in the debate on GDTs, namely to refer to geographical, affected, cultural, and political communities. Nonetheless, this is not always made explicit. Moreover, different types of community may overlap: a geographical community may for instance also be a political community that in turn consists of several cultural communities. These reflections also raise the question how this diversity of definitions should be approached.

Some authors have attempted to resolve the unclarity around the term community by proposing one definition that should be leading from now on. Resnik, for instance, argues that while we sometimes refer to communities in terms of their cultural or political characteristics, community engagement should rather focus on geographic, affected communities (9,18). In our view, the definitional issues surrounding the term community can and should not be resolved by adopting a single consistent definition. As we will substantiate in what follows, this would overlook that there can be different rationales for community engagement that require a different definition and delineation of the community. To obtain clarity about *who* to engage and which definition to adopt in which context, it is essential to first have clarity about *why* the engagement should take place and what its rationale is (14,58). Next to this, whether a group of individuals can be considered a particular type of community may guide how community engagement can be executed.

Different rationales for engagement warrant engagement of different communities

As was discussed in the introduction, the GDT literature provides a range of rationales to engage communities. These rationales, which are not mutually exclusive, can help

28 At the same time, Resnik explicitly states that he considers it most appropriate to focus on geographic communities in the context of field trials with GM mosquitoes, see section 4 for further reflections on this matter.

to define and delineate the community that should be engaged. In what follows, various examples will be discussed to illustrate this.

First, when engagement is carried out because it would lead to *better (informed) decisions* by preventing researchers from missing essential information, making incorrect assumptions or preventing bias, this could warrant involving those people with the most relevant experiential knowledge (58). In the case of GDT field trials to counter vector-borne diseases, this could be accomplished by focusing on engaging the affected community, whose members have unique expertise regarding what benefits and risks matter to them. Incorporating their views could lead to enhanced protection as members of the affected community could identify risks or harms or suggest potential ways to mitigate these that may have been underappreciated as well as enhance benefits and ensure the research is relevant to them (27,59–62). In terms of subsequent delineation, it would be key to map these different ways of being affected and engage individuals with a diversity of experience so that a range of viewpoints and information could be taken into account (58). In doing so, it may be important to consider whether the affected community consists of different cultural communities that could have different values, norms or traditions that are relevant to take into account in decisions about the development and potential deployment of GDTs. It would not be necessary (and perhaps, given the inherent diversity among members of affected communities, not possible) to focus on individuals that politically represent the affected community, nor to engage all members.

Second, when engagement is carried out with the rationale of *preventing resistance from the community or the rationale of enhancing trust*, this might be accomplished by engaging members of the geographical community (63). After all, any individual living near a field trial could influence the community's resistance or trust; it is not a priori relevant whether these individuals are affected by the trial or whether they belong to a particular cultural or political community. In terms of further delineation, it could be particularly important to include those members of a geographic community that have a large impact on other community members, such as individuals that have a prominent role in historical or traditional structures of leadership and authority (64). Similarly, those who openly support or criticize the research under consideration in the public arena and in that sense have a large impact on other community members would be important to engage.

Third, when engagement is carried out with the rationale of *safeguarding procedural justice and increasing legitimacy by involving people in decisions that affect them*, this points towards engaging the affected community. In terms of further delineation, this rationale makes it especially important to specify how those affected should be identified. If a very broad or unclear conception is adopted, the 'affected community' may become infinitely large. It is – to paraphrase an example that was previously used by Carolyn Neuhaus (48) – questionable whether it is reasonable and fair to give a

person in Siberia (who is affected in the sense that a potential field trial with gene drive organisms in Uganda is contrary to his convictions about the role of humans in nature) the same say in decision-making about this field trial as someone that lives in a vicinity of an insectary in Burkina Faso where the field trial would be carried out. To delineate the most ethically relevant group to engage, a formal impact analysis can help to substantiate and explicate who is likely to be affected in what way (27).

Finally, when engagement is carried out to contribute to *restorative justice*, this could be accomplished by engaging the cultural community (or communities) that have a shared history of past harm or historical injustices in decision-making procedures in particular research settings (16). This could be of relevance in the context of GDT field trials since various countries where GDTs are considered have a colonial past with such precedents of unjust decision-making (7). If engagement is carried out with this rationale, it has been argued to be essential to first identify the precise wrong that occurred in the past. If this past wrong consisted of a particular cultural community being excluded from decision-making and being prevented from building and maintaining decision-making structures and institutions that incorporate their values, they or their descendants should be engaged in a way that assists this community to do so in this research context. In subsequent delineation, this could for instance be accounted for by giving this community the power to determine how boundaries of inclusion in engagement with their community are drawn.

The type of community can guide community engagement

Once the relevant overarching community has been defined, an important question is whether and how its characteristics can provide further guidance to its precise delineation and help determine which engagement strategy to adopt in the specific context where GDT field trials are considered. Should the (absence of) particular characteristics lead us to lower our expectations of what community engagement may reasonably achieve, or should it rather set limits on what research may be conducted in particular communities?

Some authors on research ethics argue that the characteristics of a community can restrict what community engagement may achieve. According to Charles Weijer and Ezekiel Emanuel, for instance, community consent – one of the proposed ways of engaging communities to increase the legitimacy of decision-making by involving people in decisions that affect them – "*is only possible if the community has a legitimate political authority, which could be a legislative assembly, major, or tribal council that has the authority to make binding decisions on behalf of its members*" (p. 1143) (32). If not, they argue it is neither morally nor practically feasible to obtain such community consent. Some GDT experts, in turn, might take the absence of a shared and legitimate political authority as a reason never to consider the release of gene drive organisms in that context, since formal community consent could not be provided (7). On this view, GDT research and/or deployment could be considered unethical in a context in which the conditions are not right for community members to provide consent in this way.

However, as Weijer and Emanuel also stress, the absence of particular community characteristics does not undermine the importance of respecting and engaging communities (32). If a community is not a political community, this could also be seen as a characteristic that places an additional obligation upon researchers to ensure legitimate decision-making in other ways – effectively allowing a particular community to become a political community. As Pepijn Al has argued, the absence of existing political structures may provide reason to set up structures to use a deliberative approach to community engagement (65). In this case, it should be recognized that some ways of obtaining community consent may be more time- and resource intensive than in a community that already has a shared and legitimate political authority in place. As Gregory Kaebnick has argued in the context of broad public deliberation about gene editing in the wild, the time- and resource intensiveness of setting up novel and broad engagement strategies can generate risk-risk tradeoffs: "*there are risks to proceeding with gene editing in the wild without [such engagement strategies], but there are risks to requiring [them] as well"* (S37) (66). These trade-offs are especially significant if the problems for which GDTs are proposed to be used are very pressing. At the same time, the time- and resource intensiveness of setting up novel and broad engagement strategies does, in line with Al's argument (65), not mean that community engagement should not be carried out. Instead, this trade-off can provide an argument to focus engagement strategies on those that would be *most* impacted by the research (27) or to let the characteristics of the community in the specific context where GDT field trials are considered guide its precise delineation and help determine which engagement strategy to adopt. For example, if the affected community is engaged with the rationale of safeguarding procedural justice and increasing legitimacy by involving people in decisions that affect them, the subsequent delineation of the affected community may be determined by whether an affected community is also a political community that already has decision-making structures in place. If so, the boundaries of this political community could guide how the precise boundaries of in- and exclusion for community engagement are drawn. Similarly, if the community in question commonly relies on a particular decision-making procedure, this may provide a prima facie reason to use this procedure to engage the community.

Conclusion and future directions

While there is broad agreement about the importance of engaging community members in GDT research, disagreement and unclarity exist about how the community should be defined and delineated in this context. In this paper, we provide initial guidance on how to tackle this 'boundary problem' – how boundaries of in- and exclusion in community engagement should be drawn – in the context of GDTs. Doing so is important because it is necessary to design effective and just community engagement strategies, to evaluate them, and to prevent failed expectations. We demonstrated that the 'community' is often ill-defined and that different definitions – geographical, affected, cultural, and political communities – are used and intermingled in the debate on GDTs. We proposed to depart from the rationale for engagement, which can help to define and delineate the relevant community. Moreover, we demonstrated that the characteristics of the community itself can guide the effective design of community engagement strategies: these can provide reason to use particular community decision-making procedures that are already in place or to focus engagement strategies on those that would be most impacted by the research.

These considerations provide guidance for GDT research projects that propose engagement strategies and for the institutional ethics committees that must evaluate and approve these. To start, it is essential that the definition and delineation of the community are explicated in a research proposal in as much detail as possible, such that these can be evaluated. Moreover, it is key to provide clear argumentation why the community is defined and delineated in a certain way, so that communities themselves, other stakeholders and institutional ethics committees can evaluate and provide input on the choices that are made in doing so. Of course, there is no 'one size fits all' approach to guide engagement; engagement often has multiple rationales and potentially different rationales in different stages of research, which may warrant engagement of different communities. Next to departing from the rationales for engagement, scientific considerations such as the potential dispersal and persistence of the GDT in question, the mosquito strain and the findings of a formal impact analysis can help to substantiate the choices made.

While these considerations provide initial guidance in tackling 'the 'boundary problem', there are still several open questions that would be relevant to explore in future research. A first is a further examination of how 'affectedness' should be interpreted in the context of GDTs. Unclarity exists about the relevant interests and in what way people should be affected to consider someone a part of the 'affected community'. Second, it may be questioned whether the discussed rationales for community engagement are also legitimate. Third, the boundary problem is pertinent to community engagement strategies beyond GDTs, raising questions about how the considerations discussed here are relevant to other research contexts. Finally, of course, the proof of the pudding is in the eating, i.e. whether the input of the engaged community is eventually incorporated in research choices. GDT research projects should not just define and engage communities and invite their input, but also specify and communicate upfront how this input will be honored (67).

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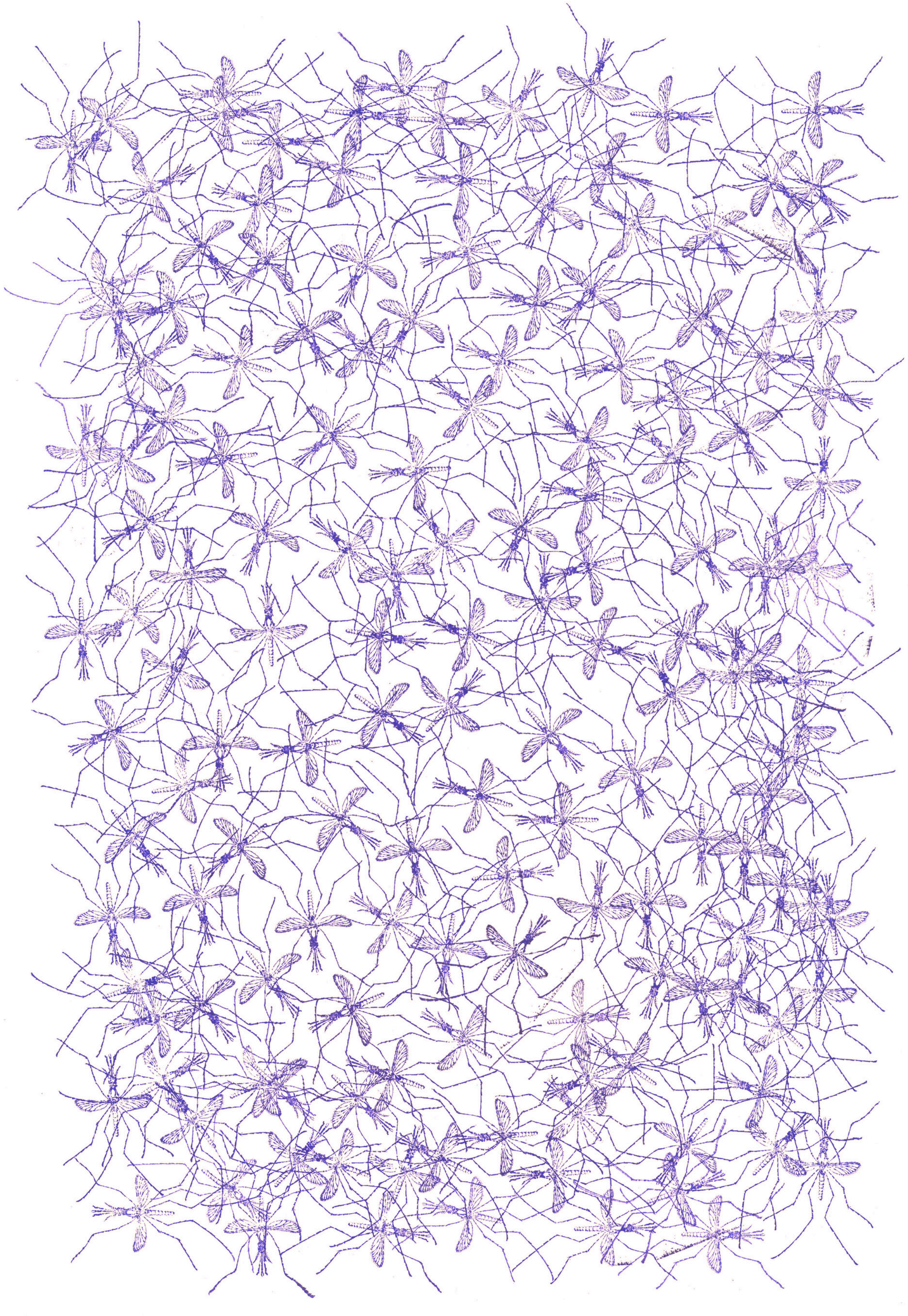
III

GENERAL DISCUSSION



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GENERAL DISCUSSION

Gene drive technologies (GDTs) promote the progressive spread of a particular genetic element within a population of non-human organisms. If successful, these technologies may help target vector-borne disease, invasive species, and agricultural pests: intractable problems with large negative impacts on human health, biodiversity, and food security. At the same time, these technologies raise important ethical questions and challenges, some of which are analyzed in this thesis. It is important to identify and evaluate the ethical challenges of GDTs in an early stage of technological development so that the findings can still inform the design of these technologies and related governance procedures and help to guide decisions about whether (and if so, under what conditions) it is morally permissible to conduct field trials with gene drive organisms. The research questions of this thesis were: (1) what are the ethical challenges of GDTs? and (2) how can GDTs be developed and governed in an ethically responsible way?

In this final chapter, I will first answer these research questions by summarizing and elaborating upon this thesis' main findings. Subsequently, I will place these findings in a broader perspective to determine what lessons can be learnt for ethics parallel research as an approach for early ethical guidance of new and emerging technologies more generally. Finally, I will summarize the main conclusions and formulate key recommendations to guide the ethically responsible development and governance of GDTs.

What are the ethical challenges of GDTs?

The first research question of this thesis concerns the ethical challenges of GDTs, inviting an exploration of the 'ethical landscape' of GDTs. Just like geological landscapes do not appear out of nowhere but have instead been shaped and influenced by all kinds of past processes, the ethical landscape of GDTs has been shaped and influenced by discussions on previously developed, related technologies such as genome editing technologies. As has been argued previously, these 'landscapes' share similar features. Analyzing previous discussions on genome editing technologies can therefore help to think about the ethical challenges of GDTs (1) (Chapter 2). However, much in the same way that it is impossible to grasp a geological landscape by merely reading about it, an analysis of the ethical landscape of GDTs that limits itself to a study of the literature may miss important ethical considerations. For this reason, the identification of the ethical challenges of GDTs was also informed by empirical ethics research with a wide range of GDT experts (Chapter 3 and 4). In what follows, I will discuss the ethical challenges that were identified in these explorations of the ethical landscape of GDTs.

Learning from the past

A first ethical challenge that can be identified relates to accounting for potentially morally relevant differences between different (applications of) GDTs in their ethical analysis. Chapter 2 provided a comprehensive overview of the arguments raised in the academic discourse on genome editing in non-human animals (from here on: animals). The reasons for and against genome editing in animals relate to seven broad themes: human health, efficiency, risks and uncertainty, public acceptability, animal welfare, animal dignity and species-specific capacities, and environmental considerations. Many of the identified arguments are not reasons for or against all uses of genome editing in animals, but apply only to particular applications of genome editing, underlining that different ethical considerations may apply to different applications of GDTs. The ethical evaluation may be different for applications that use different gene drive designs (e.g. self-limiting vs. self-sustaining GDTs), for applications intended for use in different organisms (e.g. mosquitoes vs. rodents) or different ecosystems (with different organisms, food webs, and geographical characteristics) and for applications with different aims (e.g. to decrease vector-borne diseases in humans vs. to target invasive species). In other words, an ethical analysis of GDTs should take these potentially morally relevant differences into consideration. Doing so facilitates ethical analysis that is situationally embedded and avoids overly generalizing ethical speculation (2,3). To draw conclusions about the ethical acceptability of a field trial with gene drive organisms, for instance, its specific context should be stipulated and evaluated to assess whether and how it impacts the ethical analysis. As this PhD thesis aims to identify and evaluate the ethical challenges of GDTs *generally* rather than limit itself to one specific application, it by and large does not draw blanket statements about the moral (un)acceptability of (the deployment of) these technologies, but rather stipulates conditions that should be met to develop and govern these technologies in an ethically responsible manner. Chapter 6 zoomed in on one specific application in mosquitoes and draws conclusions about the prima facie moral permissibility of applying GDTs to alleviate the burden of malaria.

A second ethical challenge that should be addressed relates to who contributes to and impacts the evaluation of GDTs and their ethical and societal implications. To start, Chapter 2 pointed out that the academic debate on genome editing is characterized by a low disciplinary diversity. The large majority of authors of articles that were included in our systematic review were life scientists who investigated the technical feasibility of genome editing in animals. The academic debate on GDTs, similarly, is mostly shaped by life scientists (4) who also frequently address the ethical and governance implications of GDTs in their publications. On the one hand, this is important and encouraging as it demonstrates that these scientists acknowledge and reflect upon the ethical implications of the technologies they develop. At the same time, these publications may focus on selective ethical aspects, such as the risks of

GDTs and related biosafety and biosecurity considerations (5–9). In other words, the 'hard impacts' of GDTs may receive a lot of attention, while their 'soft impacts' – their effect on our experiences, perceptions, actions, social structures and/or moral values – may be overlooked (10,11). Similarly, life scientists may be more inclined to assess the (un)suitability of existing risk assessment and governance frameworks than to assess whether and under what conditions gene drives could be developed and governed in an ethically responsible manner (4). As the debate on GDTs moves towards potential field trials and real-world applications, academic experts are likely to have a prominent impact on related policy and governance decisions (12,13). In this process, it is especially important that the development and governance of GDTs are guided by an interdisciplinary evaluation of these technologies and their ethical and societal implications. In Chapters 3 and 4, the moral views of experts from a wide range of disciplines were explored. The findings confirmed that professionals from different disciplines contribute different insights and perspectives, underlining the importance of interdisciplinary collaboration.

Moreover, Chapter 2 also demonstrated that there is a disjunction between the public and academic debate on genome editing in animals. Various public concerns – for instance related to equity of access to the potential benefits, the just distribution of governmental funding, and the commercialization of genome editing technologies – were largely absent from the academic debate. In recent years, a few studies have been published on public views on the use of genome editing and GDTs in wildlife (14–16). In these studies, respondents amongst others raised concerns that genome editing of wildlife messes with nature (15). Moreover, public attitudes depended to a large extent on whether a self-limiting or self-propagating GDT would be used, whether native or non-native species would be targeted, and whether it would replace or suppress the target species (17). All in all, these public views express relevant questions regarding the role of humans in nature and the value of species that have thus far been underexplored in the academic debate on GDTs. In Chapter 6, this issue was evaluated in more detail. Moreover, Chapter 5 presented photographs and accompanying questions that could be used to incite public reflection on the impact that GDTs may have on our lives and the world around us (18).

Finally, a third ethical challenge relates to what kind of arguments are taken into consideration in the ethical analysis of GDTs. Chapter 2 demonstrated that many arguments in the academic debate on genome editing are consequentialist, while other relevant types of considerations – such as duty and virtue ethical considerations – remain underexposed. The academic debate on GDTs shows a similar trend (4). It was also demonstrated that the academic debate on genome editing has given relatively little consideration to animal ethics; there was, for instance, relatively little reflection on how the interests of animals are impacted by genome editing and whether it matters morally which species is used in genome editing experiments. While a few papers on animal ethics considerations related to GDTs have been published (19–21), these considerations similarly remain underrepresented in this context. As was mentioned in the introduction, the fact that GDTs are intended for potential use in wild organisms rather than cultivated crops and laboratory and farm animals raises specific ethical questions with regards to whether and if so, under what conditions humans should intervene in nature in this way. To reflect on these questions, it is essential to include a broader range of ethical considerations than the consequentialist and human-focused ones that tend to dominate the current debate (4). Chapter 6 intended to broaden the debate by evaluating the application of GDTs to target malaria from a biocentric perspective.

Substantive and procedural ethical challenges of GDTs

The empirical ethics research amongst GDT experts from a variety of disciplines (Chapter 3 and 4) led to the identification of additional substantive and procedural ethical implications and challenges of GDTs. In what follows, the identified challenges will first be summarized descriptively. In the next section, several of these challenges will be evaluated normatively to draw conclusions about the ethically responsible development and governance of GDTs.

With regards to the substantive ethical issues – i.e. those questions, concerns, and implications that relate to "*what is right in terms of duties, rights, and values (..) independent of any decision-making procedure*" (p. 155) (22) – three ethical challenges were identified. The first substantive ethical challenge concerns how the uncertainty related to GDTs should be approached. Chapter 3 outlined various sources of uncertainty, including technical hurdles that have been encountered in making stable GDTs, knowledge gaps related to the efficacy and risks of GDTs and the dynamics and ecosystem functions of populations in which GDTs would be used, and the complexities involved in translating results of laboratory experiments and mathematical modeling to the field. Despite agreeing about these sources of uncertainty, the respondents in our interview study disagreed about whether this uncertainty provides a rationale to refrain from field trials or to proceed with phased testing to obtain more knowledge given the harms of the status quo.

The second substantive ethical challenge of GDTs relates to how alternative strategies should be weighed in the moral evaluation of GDTs. Chapter 3 showed that respondents in our interview study commonly evaluated GDTs by comparing them to alternatives, albeit different ones. Some respondents compared GDTs to conventionally used strategies to target vector-borne diseases, invasive species, and agricultural pests such as bed nets, insecticides, and pesticides. These respondents generally argued that these 'downstream' approaches are currently not successful in targeting these major problems, and that some of these approaches – such as insecticides and pesticides – are moreover harmful to the environment, other species and/or humans. According to these respondents, this provides a prima facie reason to develop innovative strategies such as GDTs to tackle these problems. Other respondents instead compared GDTs to systematic changes – 'upstream' solutions – in our global health care, political and agricultural systems. These respondents argued that vector-borne diseases, invasive species, and agricultural pests are the result of underlying problems in these systems, and that we should thus look at the solution at this level rather than trying to 'fix' them at a superficial level with a technological solution.

The third substantive ethical challenge regards how nature should be viewed and whether the use of GDTs is compatible with the role that humans should have in nature. Some respondents in our interview study (Chapter 3) argued that GDTs would disrupt the natural state of affairs in problematic ways or be a continuation of the problematic and unbalanced way in which humans treat the world around them. Other respondents questioned these positions by raising questions about how nature should be viewed and defined, whether a 'natural' state of affairs exists in the first place, and how the value and interests of humans, non-human animals and the environment should be balanced. Whereas some respondents argued that human interests should take precedence over the interests of animals and the environment in decisions about GDTs, other respondents disagreed, leading to different views on the moral permissibility of applications of GDTs. In Chapter 6, we morally evaluated this matter. In doing so, we adopted the most encompassing perspective on which organisms possess inherent worth – i.e. a biocentric perspective that attributes *equal* inherent worth to all life forms – to draw conclusions about the moral permissibility of using GDTs to target vector-borne diseases in mosquitoes.

Three additional ethical challenges were identified with regards to the procedural ethical issues – i.e. the questions, concerns, and implications that relate to the process of governance of and decision-making about GDTs. The first procedural ethical challenge relates to who should be engaged in decision-making about GDTs, what they should be engaged in and in what way. As Chapter 4 demonstrated, respondents generally agreed on the importance of engaging communities, stakeholders, and broader publics, yet disagreed on the reasons for and timing and design of such engagement. Chapter 8 provided initial guidance for deciding who should (not) be engaged in decision-making about GDT field trials. Additionally, respondents in our interview study identified various complexities related to engagement that should be addressed, including the conflicts of interest that could be involved if engagement processes are led by GDT scientists, the time and resource intensiveness of engagement, and the difficulties involved in taking the input obtained in engagement into account in subsequent decisions regarding GDT development and governance.

The second procedural ethical challenge regards the power dynamics that may be involved in GDT research and how these might best be mitigated. Power dynamics may be present in any research context, but may be particular pressing in the context of GDTs. This may be so because GDT research has commonly been initiated by scientists from high-income countries (HIC), yet potential deployment is predominantly considered in low- and middle-income (LMIC) countries where large social and economic inequalities exist. Moreover, power dynamics could be particularly pressing in countries with a history of (colonial) injustices in decision-making. These inequalities and historical injustices could threaten ideals of co-development and fair partnership in the context of GDT research. Next to this, this challenge also evokes discussion about whether and if so, to what extent (foreign) researchers can place demands on the decision-making and governance procedures that should be in place to develop and govern GDTs in an ethically responsible way.

The third procedural ethical challenge concerns the governance structures that should be in place to make decisions about GDTs. Chapter 4 identified different stances with regards to whether these governance structures should or should not be similar to those used for other area-wide interventions, such as building a large dam or a nuclear power plant or spraying pesticides or insecticides over large areas of land. Those respondents that considered GDTs to have unique characteristics – such as the high level of uncertainty and risk involved with their deployment – compared to other area-wide interventions argued that different decision-making procedures should be in place than those that are commonly used for these kinds of decisions, whereas those that did not consider GDTs to have unique characteristics disagreed. Other respondents argued that the way decisions about area-wide interventions are made is generally insufficient, and that governance procedures should generally be improved. Relatedly, respondents had different opinions regarding what decision-making model should be used to decide about eventual deployment of GDTs in field trials: direct democracy approaches, deliberative democracy approaches, or decision-making by representatives. In Chapter 7 we analyzed the use of patents as a method for 'private governance'. Private governance occurs when certain phenomena, such as the use of new biotechnologies, are regulated by private actors rather than through governmental policies. Patents are 'rights of exclusivity' and can thus also be employed to achieve private governance (23). In the context of GDTs, researcher Kevin Esvelt proposed using gene drive patents to prevent others from using this technology without disclosing their research plans and accompanying safety and ethical issues (24,25), raising the question of whether this can be ethically justified or not.

How can GDTs be developed and governed in an ethically responsible manner?

Overall, the analysis of the identified ethical challenges led us to draw various conclusions regarding how GDTs can be developed and governed in an ethically responsible manner. In what follows, these will be discussed in relation to various overarching themes: benefits, risks, and uncertainty; the moral (im)permissibility of a technofix; the role of humans in nature; community and stakeholder engagement; and decision-making.

Benefits, risks, and uncertainty

As GDTs are intended for ecosystem management and could thus have a plethora of different effects on human health, animals and the environment, it is essential to assess and evaluate their potential positive and negative effects in the short as well as in the long term. Chapter 2 demonstrated that many arguments in the broader academic debate on genome editing are consequentialist, yet there is a scarcity of systematic comparisons of potential consequences of using these technologies. As was pointed out in Chapter 3, the debate on GDTs is also prone to focus on views that either draw a picture of GDTs as silver bullets that could be a cure-all for vector-borne diseases (26) or as technologies that are bound to have disastrous and irreversible consequences (27). To prevent such a false dichotomy in the ethical assessment of GDTs, it is essential to systematically assess and compare all their benefits and harms to draw conclusions about the best *overall* consequences. We have argued the principles of proportionality and subsidiarity should be applied to do so. The principle of proportionality entails that the potential benefits of GDTs should be weighed against their potential harms or risks. The principle of subsidiarity implies that a policy should only be adopted if there is no less harmful policy that would achieve the same result. In other words, applications of GDTs should be compared to alternative policies in terms of potential harms and benefits, including the status quo with its harms and benefits. If GDTs are considered to target vector-borne diseases, for instance, unintended negative ecological effects could be a pressing concern, warranting a thorough inventory of related risks and harms. When weighing these risks and harms, the principle of subsidiarity requires us — among other things — to balance these possible negative ecological effects with the deaths caused by these diseases and the negative ecological effects of continuing to use insecticides.

When it comes to assessing and evaluating the potential risks and uncertainty related to new and emerging technologies, the precautionary principle is also often invoked. Indeed, it has been argued that the precautionary principle "*lies at the heart of international governance of GMOs [genetically modified organisms] under the Cartagena Protocol*" (p. 2) (28). Similarly, the Ad Hoc Technical Expert Group (AHTEG) to the Convention on Biological Diversity (CBD) stated that "*a precautionary approach and cooperation with all countries and stakeholders that could be affected (..) might be warranted in the development and release of organisms containing engineered gene drives, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity*" (p.5) (29). At the same time, many versions and interpretations of the precautionary principle exist, complicating its straightforward application (30,31). Moreover, the precautionary principle has been subject to extensive debate on the potential negative effects that could result from its application, such as that it could require unreasonable sacrifices in the name of safety (32) and could stifle innovation and scientific progress (33). Indeed, focusing purely on the potential safety risks of GDTs may have large opportunity costs – i.e. costs associated with *not* using GDTs – that should also be considered in determining the best course of action. In Chapter 3, we therefore argued in favor of specifying supposed precautionary courses of action as precautionary "*with respect to something*" (p. 469) (34), and looking for a middle ground of 'optimal' rather than 'maximum' precaution (35). In doing so, it is essential to distribute the burden of proof with regards to 'proving' certain risks or harms among those that propose to deploy GDTs and those that oppose such deployment. Just like it is not possible to prove that all ravens are black unless one is able to determine the color of all existing ravens, it is logically impossible to provide a proof of non-harmfulness of a technology unless all its possible effects are determinable and known (30). As this is not the case, we instead need to look for reasonable grounds for concern about the possible harmfulness of GDTs. In identifying and examining the risks and harms of GDTs potential 'pathways to harm' should be formulated, which should be investigated in detail by the responsible regulators and scientists.

Finally, Chapter 3 showed that it is essential to address and be open about existing knowledge gaps and technical hurdles related to GDTs. We argued that expectations about GDTs are 'performative': they are not just descriptions of possible futures, but actively shape the future, for instance affecting agenda setting, resource allocation and calls for open field trials (36–41). Setting realistic expectations is thus important to prevent potential harm that could result from premature field trials and the injustices that could result from disproportional research spending on GDTs compared to alternative strategies to tackle vector-borne diseases, invasive species, and agricultural pests.

The moral (im)permissibility of a technofix

The reflections on setting realistic expectations as well as the evaluation of potential alternative strategies to target vector-borne diseases, invasive species, and agricultural pests also raise the question whether it is morally permissible to resolve these issues using a 'technofix'. While one could conceive of vector-borne diseases, invasive species, and agricultural pests as biological problems – in the case of vector-borne diseases for instance caused by the presence or absence of malaria parasites in mosquitoes – Chapter 3 illustrated that these problems are sustained due to social, economic, and political factors. In the case of vector-borne diseases, for instance, there is a strong relationship between socioeconomic status, the availability of health care facilities and the removal of stagnant water on the one hand, and the morbidity and mortality of malaria on the other. If more was invested to improve the social determinants of health, the impediments of vector-borne diseases would be much lower (42,43). By reducing a social problem to a technical problem, it has been argued, the application of GDTs may perpetuate these underlying problems (44–46) while problematic side-effects get free roam (44).

These criticisms provide important insights that should be taken into account to develop and govern GDTs in an ethically responsible way. Just like medical doctors learn to question 'why is this patient here, in front of me, at this moment, with this complaint?', the continuing existence of for instance vector-borne diseases – despite huge investments and worldwide efforts – raises the question: why do these diseases continue to cause deaths in particular countries, in this day and age? In doing so, historical analyses of global health investments and strategies also provide important lessons. As Randall M. Packard has convincingly argued, past health interventions have often focused on preventing or eliminating health problems one at a time, rather than looking at strategies that could address underlying socioeconomic factors and support the development of basic health services and thereby tackle various health problems at the same time (43). Moreover, the insights of local communities were often overlooked in determining the best course of action, and these communities were sometimes even constructed as being incapable of taking responsibility for their own health (43).

At the same time, these criticisms do not provide principled arguments against using GDTs. Although much can be learnt from the development and use of previous 'technofixes', they have also had overwhelmingly positive effects: interventions such as vaccines, drugs and bed nets have let to the treatment and prevention of many specific health problems and saved countless lives (43). Instead, these criticisms and lessons from the past point towards conditions that should be in place to assure GDTs do not become a problematic technofix. A first condition relates to the narrative that surrounds these technologies and the responsibility to be open about uncertainty and knowledge gaps. The feasibility of GDTs needs to be critically assessed and the technical solution should not be presented as a simple panacea to some of the world's most complex problems. Instead, it should be conceived as a potential piece in the large and difficult puzzle that could help to tackle this problem. A second condition is that (technical and social) alternative solutions to the problem should be considered, e.g. applying the principles of proportionality and subsidiarity as was argued previously. Third, *if* GDTs are deployed, the approach to tackling these problems should remain multifaceted: a range of interventions – particularly those that address other health and socioeconomic problems at the same time, should be maintained and/or intensified alongside the technological intervention. In the case of malaria, these interventions may include general investments in health care facilities, efforts to tackle poverty and education as well as continued provision of bed nets and malaria tests and treatment.

The role of humans in nature

Views of nature and what is 'natural' influence views on a broad range of emerging technologies and have long since led to debate about the ideal of nature and the (ir)relevance of naturalness as an ethical criterion (47–49). This raises questions with regards to what role these considerations should play in discussions about GDTs, as well as about how they affect the moral permissibility of GDTs.

While the former question was not addressed in detail in this thesis, it was the prime focus of a report that was written alongside this PhD thesis (50). In this report, it was demonstrated that references to nature and (un)naturalness in the literature on genetic modification often function as placeholders to convey different underlying values. Specifically, references to nature and (un)naturalness often express underlying concerns or values regarding (1) the safety and uncertainty of technological interventions, (2) the moral status, intrinsic value or integrity of the modified entities, or (3) the appropriate attitude or role of humans. Some philosophers have argued that the ambiguity of what is meant by nature and (un)naturalness and logical inconsistencies present in related discussions provide reason to ban naturalness arguments from ethical discussions about new and emerging technologies (51,52). In contrast, we instead argued that such a strategy is not only highly unlikely to succeed but would also constitute throwing out the baby with the bathwater. Instead, the relevant underlying values that are expressed in such argumentation should be identified, investigated and discussed rather than banned from the discussion (50).

In discussions about GDTs, it has also been contended that perspectives on nature and the role of humans in nature are a key theme (27,28,36,44,53). As we argued in Chapter 3, stances about the permissibility of intervening in nature in this way depend on convictions about the moral status or intrinsic value of different organisms and holistic entities, what duties we have towards these different entities, and how these duties should be prioritized if they conflict. In Chapter 6, these matters were investigated in more detail with the aim of analyzing the moral permissibility of intervening in nature in this way to target malaria. Various perspectives on which organisms matter morally for their own sake were outlined, after which the most encompassing perspective on which organisms possess inherent worth was adopted for the sake of argument. According to this biocentric perspective, equal inherent worth should be attributed to all life forms. Subsequently, it was argued that even if this most encompassing perspective is adopted, the moral worth of individual mosquitoes does not provide reason to refrain from using GDTs to alleviate the burden of malaria. Our ethical analysis showed that this context invokes the principle of self-defense, which overrides the prima facie concerns that a biocentrist would have against the use of GDTs. This led to the conclusion that, as long as humans cannot reasonably avoid being exposed to malaria mosquitoes and there is no available alternative that is known to be more or equally effective but to cause less harm to mosquitoes, these considerations do not provide overriding arguments against the deployment of GDTs to alleviate the burden of malaria.

Community and stakeholder engagement

With regards to community and stakeholder engagement, various recommendations can be made regarding who should be involved in decision-making about GDTs, by whom, and in what way. In Chapter 8, we shed more light on the 'boundary problem': the problem of determining how boundaries of in- and exclusion in community engagement should be drawn. We argued that it is important to define and delineate the community as this is necessary for the design of effective and just engagement strategies. Failing to do so may also create obstacles to determine who can represent a community and to evaluate engagement efforts, and lead to dissatisfaction and loss of trust. Subsequently, we demonstrated that the term 'community' is often used in the GDT literature without being explicitly defined or implicitly described, and that various definitions of community – geographical, affected, cultural, and political communities – are used and intermingled. While some authors have attempted to resolve the unclarity around the term community by proposing a single definition, we contended that this unclarity can and should not be resolved by adopting a single consistent definition. Doing so overlooks that there can be different rationales for community engagement that require a different definition and delineation of the community. Instead, we argued that it is essential to first have clarity about *why* the engagement should take place and what its rationale is in order to obtain clarity about *who* to engage (54,55). To demonstrate this, we showed how different rationales for engagement can help to define and delineate the specific community that should be engaged. Moreover, we argued that the characteristics of the community itself can guide the effective design of community engagement strategies.

A second and related recommendation linked to engagement is that its rationale and aim should be substantiated in a proactive manner. This is important for several reasons. To start, as was just recapitulated, the rationale of engagement can provide essential insights into *whom* should be engaged. Similarly, as was discussed in Chapter 4, it may provide insights into *when* this engagement should take place. For instance, if engagement is carried out because it would lead to better (informed) decisions by preventing researchers from missing essential information, making incorrect assumptions or preventing bias, this points towards conducting such engagement 'upstream', i.e. early on in the research process when GDTs and related governance mechanisms can still be informed by the obtained input. Moreover, stipulating what engagement aims to achieve helps to tailor the engagement strategies to achieve those goals in a meaningful and inclusive way. As was argued in Chapter 4, doing so thus helps to prevent that engagement is either tokenistic as a result of its demandingness or unfair as a result of its lack of inclusivity. Finally and relatedly, this

can allow subsequent *evaluation* of whether the aim of engagement has also been achieved. As Chapter 2 demonstrated, there is a disjunction between the public and academic debate on genome editing in animals: various public concerns were largely absent from the academic debate. Such a disjunction could be seen as problematic if the aim of engagement is to learn from and engage with the information obtained in engagement efforts. However, if this aim is not specified proactively, it can also not be evaluated afterwards, and engagement efforts may not have any real impact on decision-making.

Both in engagement with communities, stakeholders, and publics and in collaborations between scientists from different backgrounds, it is essential to acknowledge and mitigate power dynamics. Failing to do so may threaten the ideals of co-development, engagement and fair partnership (56) between GDT developers, communities and regulators. As was argued in Chapter 4, concrete ways to counterbalance power dynamics in engagement efforts include appointing independent moderators in deliberations and engagement activities, conducting research to tailor educational material and engagement strategies to diverse groups, allowing sufficient time for deliberations and giving communities and/or other stakeholders formal power in decision-making (45). Moreover, power dynamics in research collaborations between researchers from HIC and LMIC may be mitigated by explicitly acknowledging past and present social and economic inequalities, setting research agendas in collaboration, clarifying roles and responsibilities, sharing property rights and resources, and ensuring fair representation in authorship positions (57–61).

Decision-making

Finally, GDTs raise important ethical questions regarding decision-making about the governance structures that should be in place to make decisions about GDTs and their deployment.

Chapter 4 evaluated the demands that (foreign) researchers should be allowed to make regarding the way in which decisions about GDT deployment should be taken. As the findings discussed in this chapter underline, there may be a tension between respecting local decision-making procedures and the co-existing obligations to engage those that could be affected by open field trials with GDTs. In other words, it is important to safeguard important research ethics standards and rights, as well as to prevent cultural imperialism. At the same time, these concomitant obligations have the potential to be at odds with each other. This may be particularly complex given the fact that there are many open (research ethics) questions with regard to whether and how community consent should be obtained for GDT field trials (36,45,62,63). While much more could be said about this, we provided various concrete initial recommendations. To start, the identified tension may provide reason to focus discussion on or demands regarding decision-making models on the *goals* that such models should achieve, rather than the specific shape they should take. Next to this, the identified tension may be reduced by ensuring that local rather than foreign researchers are in the lead in knowledge production and the design of decision-making procedures. Unfortunately, the literature on GDTs – and this thesis is no exception – is dominated by authors from HIC, reflecting the current reality that GDT development predominantly occurs in these countries (56) while their deployment is most likely to be (first) considered in LMIC. This underscores the importance of evaluating who participants in the development of and research on GDTs and on what basis of equality (64–66).

Chapter 7 evaluated the fairness of decision-making about GDTs. Specifically, it evaluated 'ethical licensing': the use of patents as a strategy for 'private governance', i.e. as a method to direct others' use and research of the patented technology. While it is praiseworthy that GDT researchers and patent holders are concerned with the ethical use of these technologies, we argued that the proposed use of exclusivity rights for private governance (24,25) raises concerns of procedural justice. As this PhD thesis underlines, technologies such as GDTs are exceptional not only in terms of the promises they hold for fundamental research and therapeutic applications, but also in terms of the discussion and disagreement they generate about what would constitute 'socially responsible' or 'ethical' use of these technologies. By leaving the determination of what is 'socially responsible' or 'ethical' to the sole discretion of the patentee, ethical licensing through private governance raises concerns about the fairness of this decision-making process. The potential societal importance of biotechnologies such as GDTs provides a rationale to safeguard the fairness of regulatory processes for the use of these technologies. Correspondingly, we argued that a broader group of stakeholders, other than just the patentee, should have insight and influence in those terms of the license that govern acceptable uses of the technology. Furthermore, the debate about these restrictions should be made as transparent as possible, allowing the community at large to hold patentees and licensees accountable for the arrangements made. Specifically, we suggested creating a platform similar to the Creative Commons platform in the creative industry, which unites different stakeholders from this industry to formulate a model license. In the context of GDT patents, a comparable process could be facilitated by a platform that brings together stakeholders from the research community, which could then jointly formulate a guideline in which consensus is specified. This platform should be open to the public to the extent possible to allow public scrutiny of (debates on) the contents of the guideline. The best practices thus formulated could become a guideline for ethical use of GDTs and a model license for those wishing to license the technology.

Lessons for ethics parallel research as an approach for early ethical guidance of new and emerging technologies

This PhD thesis does not only yield insights in the ethically responsible development and governance of GDTs, but also provides lessons for ethics parallel research as an approach for early ethical guidance of new and emerging technologies. As was argued in the introduction, the questions and concerns that GDTs raise and expose resemble so-called 'wicked problems': problems that concern various disciplines and stakeholders and that invoke discussion and disagreement regarding what the problem is as well as what the desired solutions should be (67). The findings described in this PhD thesis underline this; GDT experts from different disciplines have diverging moral views with regards to whether and how GDTs should be developed and governed. Whereas some view vector-borne diseases as the problem and GDTs as the solution, others argue we should rather see global health inequalities and lack of proper health care facilities as the problem and look at sustainable change of global health care systems as a solution. Similarly, there is fundamental disagreement about whether some of the aims of potential GDT deployment, such as targeting invasive species, are worthwhile to pursue, and if so, whether GDTs are the best approach to achieve this aim. This polarization can also be observed in the public debate on GDTs, with some arguing that GDTs could solve intractable problems and should be developed in a phased testing approach (68,69), while others contend that there should be a moratorium on these technologies as they are too risky or ethically impermissible on other grounds (27,70,71). Given the current stage of development of GDTs – with laboratory proof-of-concept GDTs having been developed in various organisms, while potential field trials are still estimated to be years away (72) – the research presented in this thesis provides a prime example of ethics parallel research as an approach for *early* ethical guidance. Correspondingly, it is also relevant to evaluate what broader lessons and implications can be drawn from the research presented in this study for the guidance of other new and emerging technologies that are in their early stages of development. The research presented here provides at least three relevant lessons.

First, the early ethical guidance of new and emerging technologies not only necessitates a normative evaluation of the different stances and arguments put forward by different stakeholders, but also warrants a conceptual analysis of key terms that play a role in related discussions. Indeed, conceptual matters have important ethical implications. If one argues that the community should be engaged in GDT research, for instance, a further conceptualization of the 'community' and 'engagement' are necessary to determine what obligations are owed to whom. Moreover, conceptual analyses can provide insights that may help to disentangle messy debates about new and emerging technologies by demonstrating that different stakeholders are in fact concerned with different issues, even if they use the same words. If one is concerned about the impact of genetic modification on nature, for instance, one may be concerned about its impact on 'non-human nature' (e.g. organisms in the 'wild' that have not been constructed or modified by humans) or about its impact on 'human nature' (e.g. the essential characteristics that are taken to make humans human) (50) – two different concerns which warrant different normative analyses. Lastly, it may also be relevant to analyze whether new and emerging technologies should make us rethink concepts that we commonly use in our ethical thinking. It has for instance been argued that the development of ectogenesis – an 'artificial womb' – could reconceptualize 'motherhood' has a gender neutral activity (73). Similarly, it may be questioned whether genetic modification technologies should cause us to rethink the ontological boundaries between the 'natural' and the 'artificial'.

Second, the early ethical guidance of new and emerging technologies should, as much as possible, stipulate concrete moral obligations. In the context of GDT research, a few publications have outlined broad ethical principles (56,74). Claudia Long and colleagues, for instance, argue that potential field trials with gene drive organisms should conform to the principles of 'fair partnership' and 'public engagement' (56). On the one hand, stipulating such broad ethical principles can be a helpful starting point as these principles can provide a common framework of justification that can be used to guide and evaluate research, and thereby serve as a moral compass (74,75). Moreover, ethical principles can apply across nations, disciplines and legislations and can be more flexible that legislation. On the other hand, ethical principles are – by their nature – general and comprehensive norms that do not function as precise guides to action. It is important to identify principles and values, but not enough. As philosopher Stephen Toulmin already outlined in his reflections on the Belmont Report's principles for biomedical research ethics, it can be surprisingly easy to settle on general moral principles, but much harder to reach consensus on how these should be operationalized (76). 'Fair partnership', for instance, is a principle that is unlikely to lead to opposition from anyone. Nonetheless, mere agreement on this broad principle can also obfuscate underlying disagreements: what constitutes a true partnership, what makes such partnership fair, and what concrete obligations does it give rise to?

Third and finally, it is important to acknowledge that while ethics parallel research can identify important stances and arguments and provide provisionary answers as to how new and emerging technologies should be developed and governed, it will not resolve the inherent uncertainty associated with these technologies nor the controversy regarding their moral permissibility (77,78). This becomes particularly clear by looking at the example of the European market authorization of commercial applications of GM crops. This is a field of technological development that has been researched extensively, and for which participatory and deliberative activities have allowed for the mapping and evaluation of many different stances, values, hopes and concerns (79). Despite these scientific and participatory activities, controversy remains as these activities cannot conclusively answer questions such as: 'at what point is there sufficient certainty?', 'how safe is safe enough?' or 'when has a controversy been sufficiently acknowledged, deepened, or addressed to take a justified decision for a certain course of (in)action?'. As Ruth Mampuys has convincingly argued, it is essential to face the political nature of these questions and to acknowledge that explicit political deliberation is necessary to arrive at a decision (79). For GDTs and new and emerging technologies more generally, it is thus key to carefully map and analyze the different arguments, stances and sources of knowledge that may inform decision-making about their development and governance, but also to recognize that political judgement will eventually be needed to arrive at an eventual decision about their deployment.

Concluding remarks and recommendations

Much has changed since the days that Mendel studied his pea plants. Not only do we know much more about the intricacies of genetic inheritance mechanisms, scientists are also working on technologies that can drive certain genetic elements through populations of organisms. These GDTs may potentially help to tackle various intractable problems in the realm of vector-borne diseases, invasive species, and agricultural pests. At the same time, these technologies and the prospect of using them to edit organisms in our shared environment raise important ethical questions and concerns. The questions and concerns that GDTs raise and expose resemble so-called 'wicked problems': problems that concern various disciplines and stakeholders and that invoke discussion and disagreement regarding what the problem is as well as what the desired solutions should be. To disentangle these problems and discussions, this PhD thesis employed ethics parallel research to provide ethical guidance with regards to GDT development and governance in an early stage, proactively or parallel to development of the technology itself.

As GDTs are still in their early stages of development, the research presented in this thesis provides a prime example of ethics parallel research as an approach for early ethical guidance. Through literature research, empirical ethics research and normative evaluation, this PhD thesis provided a roadmap to navigate the ethical landscape of GDTs. In doing so, a wide range of perspectives were included by incorporating qualitative research with GDT experts from various disciplines and with different stances on these technologies. This has led to the identification and subsequent evaluation of a range of important ethical challenges. Based on this identification and evaluation, we have come to the following key recommendations for researchers and policymakers in the GDT field:

General recommendations
The ethical evaluation of GDTs should be situationally embedded and take into account potentially morally relevant differences (e.g. between self-limiting vs. self-sustaining GDTs, applications in different organisms and ecosystems and with different aims) to avoid overly generalizing ethical speculation.
The development, potential deployment, and governance of GDTs should be guided by interdisciplinary and proactive evaluation of these technologies and their ethical and societal implications.
(Non-consequentialist) considerations with regards to animal and environmental ethics should be an integrative part of the ethical evaluation of GDT development and governance.
Recommendations with regards to benefits, risks, and uncertainty
The benefits and harms of gene drives and alternative strategies should be systematically compared to draw conclusions about the best *overall* consequences, applying the principles of proportionality and subsidiarity.
If a certain course of action is argued to be best because it is most precautionary, it should be specified with regards to what this course of action is precautionary. The aim should be to look for a course of action that facilitates 'optimal' rather than 'maximal' precaution.
The burden of proof with regards to 'proving' certain risks or harms should be distributed among those that propose to deploy GDTs and those that oppose such deployment. In doing so, reasonable grounds for concern about the possible harmfulness of GDTs should be identified and potential 'pathways to harm' should be formulated and investigated in detail by the responsible regulators and scientists.
It is essential for GDT scientists to be open about the knowledge gaps, complexities and uncertainties involved in estimating the effects of GDTs, as expectations about new and emerging technologies are performative and overhyping can have concrete undesirable effects.
Recommendations with regards to comparing GDTs to alternative strategies
It is essential to learn from the history of global health investments and strategies, which have all too often focused on preventing or eliminating health problems one at a time, rather than looking at strategies that address underlying socioeconomic factors and support the development of basic health services.
To prevent GDTs from becoming a problematic technofix, they should not be presented as a simple panacea, be carefully compared to alternative solutions, and be part of a multifaceted approach in which a range of interventions (particularly those that address other health and socioeconomic problems at the same time) are maintained and/or intensified alongside the technological intervention.
Recommendations with regards to (un)naturalness and the (role of humans in) nature
Arguments with regards to nature and (un)naturalness express relevant underlying values that should be identified, investigated and discussed in discussions about GDTs.
Even if one adopts a biocentric perspective on which organisms have inherent worth in which equal inherent worth is attributed to all living organisms, the inherent worth of individual mosquitoes does not provide an overriding argument against the deployment of GDTs to alleviate the burden of malaria.
Recommendations with regards to engagement
Ethical issues and concerns uncovered through public and community engagement should be normatively analyzed in the academic (ethics) literature on GDTs.
To design effective and just engagement strategies, it is essential to define and delineate the community. Failing to do so can also create obstacles to determine who can represent a community and to evaluate engagement efforts, and moreover lead to dissatisfaction and loss of trust.
In determining how boundaries of in- and exclusion should be drawn in community engagement, geographical, affected, cultural and political communities should be distinguished.
The rationale and aim of public and community engagement should be substantiated in a proactive manner as this can help to determine *who* to engage and *when* engagement should take place, to tailor the engagement strategies to achieve their aims in a meaningful and inclusive way, and to facilitate evaluation of whether engagement in fact achieved these aims.
In engagement with communities, stakeholders, and publics and in collaborations between scientists from different contexts, it is essential to acknowledge and mitigate power dynamics. Failing to do so may threaten co-development, engagement and fair partnership between GDT developers, communities, and regulators.
Recommendations with regards to decision-making
To mitigate the potential tension between respecting local decision-making procedures and safeguarding important research ethics standards and rights, it is important to focus discussion on or demands regarding decision-making models on the *goals* that such models should achieve, rather than the specific shape they should take.
It is important to evaluate who participates in the development of and research on GDTs and on what basis of equality, and to ensure that local rather than foreign researchers are in the lead in knowledge production and the design of decision-making procedures.
The proposed use of exclusivity rights for private governance of GDTs raises concerns of procedural justice. Instead, a broader group of stakeholders, other than just the patentee, should have insight and influence in those terms of the license that govern acceptable uses of the technology.
Recommendations with regards to ethics parallel research as an approach for early ethical guidance
The early ethical guidance of new and emerging technologies not only necessitates a normative evaluation of different stances and arguments, but also a conceptual analysis of key terms that play a role in related discussions.
The early ethical guidance of new and emerging technologies should, as much as possible, stipulate concrete moral obligations.
To arrive at eventual decisions about deployment of new and emerging technologies, political deliberation and decision-making are necessary.

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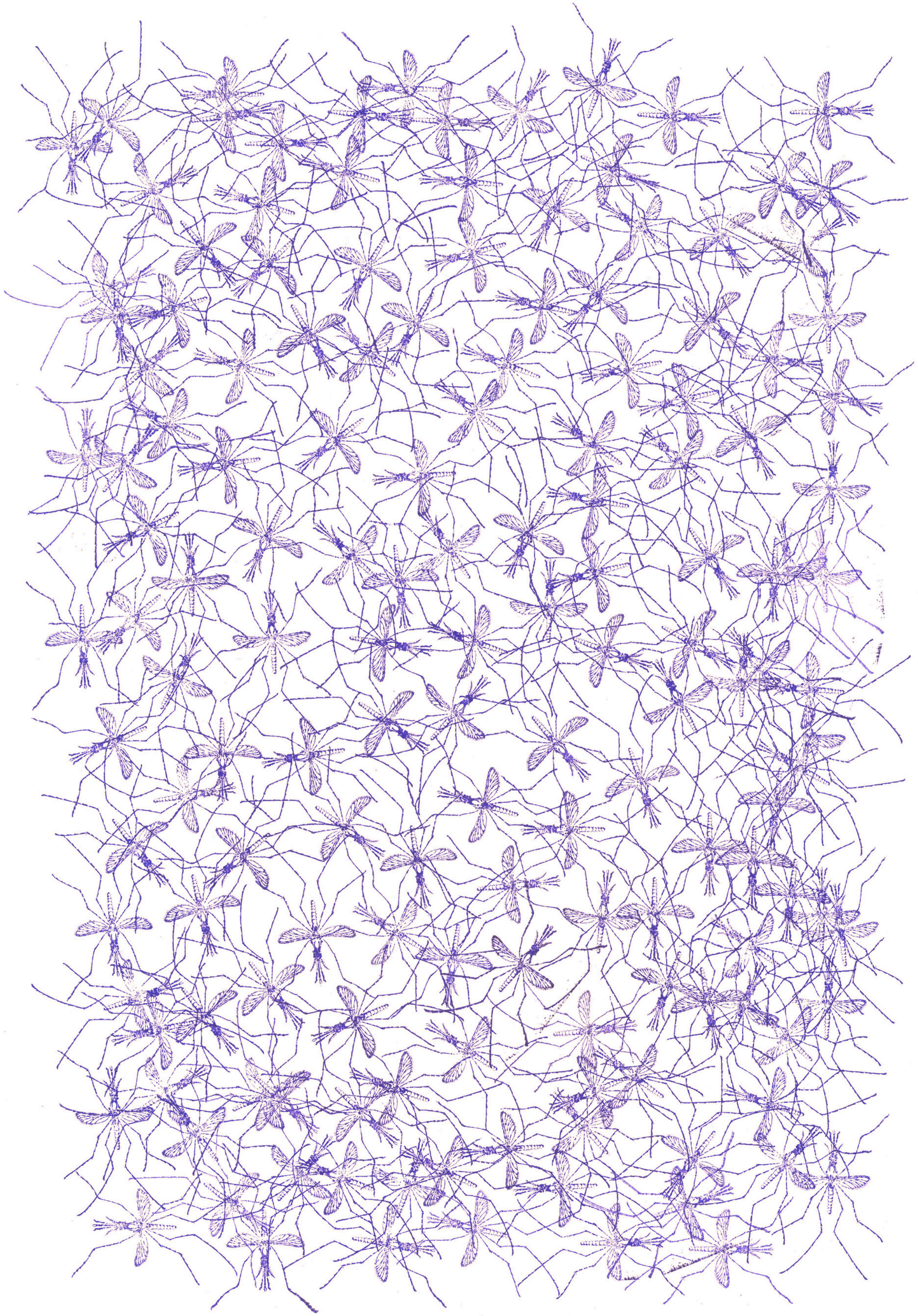
APPENDICES



Summary

Gene drive technologies (GDTs) bias the inheritance of a particular genetic element within a population of non-human organisms, thereby promoting its progressive spread across this population. So far, proof-of-concept GDTs have been developed in various organisms, and some GDTs have been tested in large indoor cages that partially mimic ecological conditions in the wild. If they are successfully further developed and deployed, GDTs could be used to tackle impactful problems that humans have thus far not been able to resolve through other means. GDTs could, for example, be used to foster public health by targeting organisms that carry infectious diseases that affect humans, such as malaria, dengue, or Lyme disease. They could also be used for ecosystem conservation, for example by targeting invasive, alien species that threaten native species and biodiversity. Furthermore, they could be deployed in agriculture to target organisms that damage or infect cultivated crops or to reduce or eliminate weeds. At the same time, the development and governance of GDTs raise a range of ethical questions and concerns that warrant proactive ethical evaluation. Amongst others, these ethical issues regard the uncertainty related to GDTs and their potential risks, whether it is morally permissible to intervene in nature in this way, and how the development, governance and potential deployment of GDTs should be guided.

The proactive identification and evaluation of these and other ethical issues related to GDTs is essential to facilitate their responsible development and governance. Therefore, the central aim of this PhD thesis is to identify the ethical challenges of GDTs and to evaluate how GDTs can be developed and governed in an ethically responsible way. To do so, this thesis answers two main research questions: (1) what are the ethical challenges of GDTs? and (2) how can GDTs be developed and governed in an ethically responsible manner? These two questions are addressed in the first and second part of this thesis, respectively.

Part I: The Ethical Landscape – Identifying the Ethical Challenges of Gene Drive Technologies

The first part of this thesis investigates the 'ethical landscape' of GDTs by identifying the ethical challenges of GDTs. Discussions on new and emerging technologies often feature similar patterns of moral argumentation. For this reason, exploring what can be learnt from discussions on genome editing more generally is relevant for the evaluation of GDTs. With this aim, **Chapter 2** presents the results of a systematic review of reasons for and against genome editing in non-human animals that have been reported in the academic literature. The reported reasons related to seven themes: human health, efficiency, risks and uncertainty, public acceptability, animal welfare, animal dignity, and environmental considerations. Our findings illuminate several important considerations about the academic debate on genome editing technologies, including a low disciplinary diversity in the contributing academics. Most articles that were included in this review were written by academics from the biomedical or animal sciences. Next to this, we concluded that there is a scarcity of systematic comparisons of potential consequences of using these technologies, an underrepresentation of animal interests, and a disjunction between the public and academic debate on this topic. In this chapter, we call for a broad range of academics to get increasingly involved in the discussion about genome editing and GDTs. We also suggest that these ongoing debates seek to incorporate animal interests and systematically compare applications of these technologies using the principles of proportionality and subsidiarity. Finally, we argue that the aims and methods of public engagement should be further discussed.

Empirical ethics research is another relevant method to identify important challenges of GDTs, and to elucidate how important stakeholders view and weigh different ethical aspects. Chapter 3 and 4 present the results of an interview study amongst GDT experts from a variety of disciplines. **Chapter 3** specifically focuses on the substantive ethical questions, concerns, and implications of GDTs, i.e. those questions, concerns, and implications that relate to "*what is right in terms of duties, rights, and values (..) independent of any decision-making procedure*". This chapter helps to disentangle the polarized debate on GDTs by providing a better understanding of the moral views of GDT experts about the permissibility of (applications of GDTs). It is shown that the respondents' moral views of GDTs were principally influenced by their attitudes towards (1) the uncertainty related to GDTs; (2) the alternatives to which they should be compared; and (3) the role humans should have in nature. We argue that scientists should be open about the knowledge gaps, complexities and uncertainties involved in estimating the effects of GDTs. Furthermore, we contend that it is important to look for a middle ground of 'optimal' rather than 'maximum' precaution and to make empirical convictions about alternatives to GDTs explicit. Finally, we suggest that it is important to critically evaluate the moral (im)permissibility of a 'techno fix' and how the value and interests of humans and non-human organisms should be balanced in decision-making about GDTs.

Chapter 4 focuses on the procedural ethical questions and implications of GDTs, i.e. the questions, concerns and implications that relate to the process of decision-making about and governance of GDTs. The identified ethical considerations related to three main themes: (1) the engagement of communities, stakeholders and publics; (2) power dynamics; and (3) decision-making. We noted that there was broad agreement amongst respondents on the importance of engagement, yet divergent views on what this should consist of. This underlines the importance of moving from general moral principles to stipulating concrete obligations. We also identified various open questions with regards to when someone has a sufficient interest or 'stake' to be considered communities or stakeholders that should be engaged, what engagement should aim to achieve, and what demands (foreign) researchers may justifiably make on the way in which decisions about GDT deployment should be taken. We argue power dynamics should be openly addressed and propose various concrete ways to counterbalance such dynamics. Moreover, we suggest that focusing on explicating the goals of governance mechanisms can help navigate the tension between safeguarding important research ethics standards and falling into the trap of cultural imperialism. Finally, we contend that it is important to evaluate what it is (if anything) that makes the development and deployment of GDTs different from other biotechnologies and area-wide interventions, and what governance measures are warranted in view of such differences.

In **Chapter 5**, the ethical challenges that are brought about by GDTs are represented in a way that sparks the imagination and that reaches a broader range of publics than academic articles: through photographs. Whereas philosophical questions are often raised and analyzed in written texts, pictures may be a more accessible and intuitive way to incite reflection on the impact that emerging technologies may have on our lives and the world around us. In this way, these photographs contribute to facilitating public awareness and debate on GDTs.

Part II: Ethical Landscaping – Evaluating Responsible Development and Governance of Gene Drive Technologies

The second part of this thesis explores what may be called 'ethical landscaping' by evaluating how the ethical landscape should be designed or influenced, i.e. whether and how GDTs can be developed and governed in an ethically responsible manner. In doing so, three specific ethical questions and concerns with regards to GDT development and governance are evaluated in more detail.

Chapter 6 analyzes the moral permissibility of using GDTs to intentionally eradicate or modify mosquitoes to alleviate the burden of malaria. A key concern in determining the moral permissibility of using GDTs regards the question how the inherent worth and interests of individual humans, non-human animals and the environment should be balanced. It has been argued that beliefs of human superiority over non-human nature should be re-evaluated and that the inherent worth of non-human organisms should also be taken into account in analyzing the moral permissibility of GDTs. This chapter engages with these concerns by evaluating whether the inherent worth of individual mosquitoes may provide reason to refrain from using GDTs. First, we outline various perspectives on which organisms matter morally for their own sake. For the sake of argument, we adopt the most encompassing perspective on which organisms possess inherent worth: a biocentric perspective that attributes equal inherent worth to all life forms. Second, we explore how conflicting claims towards different

organisms should be prioritized from this perspective and apply this to the context of malaria control using GDTs. Our ethical analysis shows that this context invokes the principle of self-defense, which overrides the prima facie concerns that a biocentrist would have against the use of GDTs. This leads us to conclude that, as long as certain conditions are met, these considerations do not provide overriding arguments against the deployment of GDTs to alleviate the burden of malaria.

Chapter 7 evaluates the use of 'ethical licensing' in the context of GDTs and other biotechnologies. Patents are 'rights of exclusivity' that can be used to achieve private governance by controlling who is allowed to get a license and under what conditions. In the context of GDT research, researcher Kevin Esvelt has proposed to use gene drive patents to prevent others from using this technology without disclosing their research plans and accompanying safety and ethical issues. We argue that while it is praiseworthy that patentees aim to pursue a socially responsible approach in their licensing agreements, using property rights in this way raises procedural justice concerns. Foundational technologies such as CRISPR (Clustered Regularly Interspaced Palindromic Repeats) and GDTs generate about what would constitute "socially responsible" or "ethical" use of these technologies. Such value pluralism poses a legitimacy problem: who should be allowed to decide this, and under what conditions? We argue that ethical licensing should foster broad debate about whether and when these epithets apply, rather than leaving it solely up to the patentee to determine this. At a minimum, such a process should allow a broader group of stakeholders, other than just the patentee, to have insight and influence in those terms of the license that govern acceptable uses of the technology. Specifically, we suggest that a platform that brings together stakeholders from the CRISPR or GDT community could formulate a model license, including considerations related to its ethical use.

Finally, **Chapter 8** analyses the definition and delineation of 'community' in field trials with gene drive organisms. An important point of discussion regarding these field trials relates to who should be informed, consulted, and involved in decision-making about their design and launch. It is generally argued that community members in particular have a strong claim to be involved in such decision-making. Yet, disagreement and unclarity exists about how this 'community' should be defined and delineated. We evaluate this 'boundary problem': the problem of determining how boundaries of in- and exclusion in (GDT) community engagement should be drawn. We argue it is important to define and delineate whom the community comprises because doing so is necessary for the design and evaluation of effective and just community interventions, and can prevent dissatisfaction, loss of trust, and conflicts between different parties involved. Subsequently, we demonstrate that different definitions of community are used and intermingled in the debate on GDTs, and argue in favor of distinguishing geographical, affected, cultural, and political communities. Finally, we propose initial guidance for deciding who should (not) be engaged in decision-making about GDT field trials, by arguing that the definition and delineation of the community should depend on the rationale for engagement and that the characteristics of the community itself can guide the effective design of community engagement strategies.

Part III: General Discussion

The third part of this thesis presents a general discussion of its main findings. **Chapter 9** answers this thesis' research questions and places its findings in a broader perspective. First, I discuss the ethical challenges of GDTs. I argue that previous discussions on genome editing technologies underline that it is essential that the ethical evaluation of GDTs is situationally embedded, is performed proactively and in an interdisciplinary way, and incorporates a broad range of ethical arguments including (non-consequentialist) considerations with regards to animal and environmental ethics. Subsequently, I identify and discuss a range of substantive and procedural ethical challenges of GDTs. Second, I evaluate these ethical challenges and formulate recommendations to facilitate responsible development and governance of GDTs. These recommendations concern the way in which the benefits, risks and uncertainty of GDTs should be approached, conditions for the moral permissibility of a technofix, the role humans should have in nature, the aims of community and stakeholder engagement, and what governance mechanisms should be in place to make decisions about GDTs. Finally, I reflect on the insights that this thesis' results yield for ethics parallel research as an approach for early ethical guidance of new and emerging technologies more generally. I argue that the early ethical guidance of new and emerging technologies not only necessitates a normative evaluation of different stances and arguments, but also a conceptual analysis of key terms. Moreover, I contend that the early ethical guidance of new and emerging technologies should, as much as possible, stipulate concrete moral obligations. Finally, it is important to keep in mind that political deliberation and decision-making are necessary to arrive at eventual decisions about deployment of new and emerging technologies. The chapter concludes with a summary of key recommendations for researchers and policymakers in the GDT field.

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Nederlandse samenvatting

Gene drive technologieën (GDT) vergroten de kans dat een bepaald genetisch element wordt overgeërfd binnen een populatie van niet-menselijke organismen, waardoor dit genetische element zich snel door de populatie kan verspreiden. Tot dusver zijn er *proof-of-concept* GDT ontwikkeld in diverse organismen en zijn enkele GDT getest in grote laboratoriumkooien die de ecologische omstandigheden in het wild gedeeltelijk nabootsen. Als het lukt om GDT succesvol verder te ontwikkelen en toe te passen, zouden deze technologieën gebruikt kunnen worden om belangrijke problemen aan te pakken die de mens tot nu toe niet op andere manieren heeft kunnen oplossen. GDT zouden bijvoorbeeld gebruikt kunnen worden om de volksgezondheid te bevorderen door organismen aan te passen die infectieziekten overbrengen op mensen, zoals malaria, dengue of de ziekte van Lyme. GDT zouden ook kunnen worden gebruikt om ecosystemen in stand te houden, bijvoorbeeld door zich te richten op invasieve vreemde soorten die een bedreiging vormen voor inheemse soorten en biodiversiteit. Daarnaast zouden ze kunnen worden ingezet in de landbouw om organismen te bestrijden die gewassen beschadigen of infecteren, of om onkruid te verminderen of uit te roeien. Tegelijkertijd roepen de ontwikkeling en het bestuur van GDT een reeks ethische vragen en problemen op die zorgvuldig moeten worden geëvalueerd. Deze ethische kwesties hebben onder meer betrekking op de onzekerheid rondom GDT en hun potentiële risico's, of het moreel toelaatbaar is om met GDT in de natuur in te grijpen, en hoe de ontwikkeling, het bestuur en de mogelijke toepassing van GDT zou moeten worden begeleid en vormgegeven.

De proactieve identificatie en evaluatie van deze en andere ethische kwesties gerelateerd aan GDT is essentieel om deze technologieën en gerelateerd beleid op een verantwoorde manier te ontwikkelen. Het belangrijkste doel van dit proefschrift is dan ook om de ethische uitdagingen van GDT te identificeren en te evalueren hoe GDT op een ethisch verantwoorde manier ontwikkeld en bestuurd zouden kunnen worden. Om dit doel te bereiken beantwoordt dit proefschrift twee centrale onderzoeksvragen: (1) wat zijn de ethische uitdagingen van GDT? en (2) hoe kunnen GDT op een ethisch verantwoorde manier ontwikkeld en bestuurd worden? Deze twee onderzoeksvragen worden behandeld in respectievelijk het eerste en tweede deel van dit proefschrift.

Deel I: Het ethische landschap – Identificatie van de ethische uitdagingen van gene drive technologieën

Het eerste deel van dit proefschrift onderzoekt het 'ethische landschap' van GDT door de ethische uitdagingen van GDT in kaart te brengen. Discussies over nieuwe en opkomende technologieën leiden vaak tot vergelijkbare ethische discussies. Daarom is het voor de morele evaluatie van GDT relevant om na te gaan wat er te leren valt van

discussies over *genome editing* in het algemeen. Met dat doel presenteert **hoofdstuk 2** de resultaten van een *systematic review of reasons* waarin in kaart wordt gebracht welke redenen voor en tegen *genome editing* bij niet-menselijk dieren in de academische literatuur zijn gerapporteerd. De gerapporteerde redenen hadden betrekking op zeven thema's: menselijke gezondheid, efficiëntie, risico's en onzekerheid, aanvaardbaarheid voor het publiek, dierenwelzijn, de waardigheid van dieren, en milieuoverwegingen. Onze bevindingen belichten een aantal belangrijke overwegingen over het academische debat over *genome editing*-technologieën, waaronder een geringe disciplinaire diversiteit onder de bijdragende academici. De meeste artikelen die in deze review zijn opgenomen zijn geschreven door academici uit de biomedische of dierwetenschappen. Daarnaast vonden we een schaarste aan systematische vergelijkingen van de mogelijke gevolgen van het gebruik van deze technologieën, een ondervertegenwoordiging van de belangen van dieren en een kloof tussen het publieke en het academische debat over dit onderwerp. In dit hoofdstuk doen we een oproep om een breed scala aan academici in toenemende mate te betrekken bij de discussie over *genome editing* en GDT. Hiernaast concluderen we dat in dit lopende debat meer aandacht geschonken zou moeten worden aan de belangen van dieren en dat de toepassingen van deze technologieën systematisch moeten worden vergeleken aan de hand van de beginselen van proportionaliteit en subsidiariteit. Ten slotte pleiten we voor nadere discussie over de doelstellingen en methoden van *public engagement*.

Empirisch ethisch onderzoek is een andere relevante methode om belangrijke uitdagingen van GDT te identificeren en inzichtelijk te maken hoe belanghebbenden verschillende ethische aspecten zien en wegen. Hoofdstuk 3 en 4 presenteren de resultaten van een interviewstudie onder gene drive experts uit verschillende disciplines. **Hoofdstuk 3** richt zich specifiek op de substantieve ethische vragen, zorgen en implicaties van GDT: de vragen, zorgen en implicaties die betrekking hebben op "wat juist is in termen van plichten, rechten en waarden (...) onafhankelijk van enige besluitvormingsprocedure". Dit hoofdstuk helpt om het gepolariseerde debat over GDT te ontwarren door inzicht te geven in de morele opvattingen van gene drive experts over de toelaatbaarheid van (toepassingen van) GDT. We tonen aan dat de morele opvattingen van de respondenten over GDT vooral beïnvloed worden door hun houding ten opzichte van (1) de onzekerheid gerelateerd aan GDT; (2) de alternatieven waarmee ze vergeleken zouden moeten worden; en (3) de rol die de mens in de natuur zou moeten hebben. We beargumenteren dat wetenschappers open moeten zijn over de bestaande kennishiaten, de complexiteit en de onzekerheden die gepaard gaan met het inschatten van de effecten van GDT. Verder stellen we dat het belangrijk is om te zoeken naar een middenweg van 'optimale' in plaats van 'maximale' voorzorg en om empirische overtuigingen over alternatieven voor GDT expliciet te maken. Tenslotte suggereren we dat het belangrijk is om kritisch te evalueren in hoeverre een 'techno fix' moreel (on)toelaatbaar is en hoe de waarde en belangen van mensen en niet-menselijke organismen afgewogen zouden moeten worden in de besluitvorming over GDT.

Hoofdstuk 4 richt zich op de procedurele ethische vragen en implicaties van GDT: de vragen, zorgen en implicaties die betrekking hebben op het proces van besluitvorming over en beleid rondom GDT. De geïdentificeerde ethische overwegingen hebben betrekking op drie hoofdthema's: (1) de betrokkenheid van gemeenschappen, belanghebbenden en publieken; (2) machtsdynamieken; en (3) besluitvorming. We stelden vast dat er onder de respondenten een grote mate van overeenstemming bestond over het belang van het betrekken van gemeenschappen, belanghebbenden en publieken, maar dat de meningen over de vraag hoe dit zou moeten worden ingevuld, uiteenliepen. Dit benadrukt dat het belangrijk is om niet alleen algemene morele beginselen maar ook concrete morele verplichtingen te formuleren. We identificeerden ook verschillende open vragen m.b.t. wanneer iemand een groot genoeg belang heeft om te worden aangemerkt als een belanghebbende of gemeenschap die betrokken zou moeten worden, wat het betrekken van deze groepen zou moeten beogen en welke eisen (buitenlandse) onderzoekers zouden mogen stellen aan de manier waarop beslissingen over GDT genomen moeten worden. Ook beargumenteren we dat machtsdynamieken openlijk aan de orde moeten worden gesteld en stellen we verschillende concrete manieren voor om een tegenwicht te bieden tegen dergelijke dynamieken. Bovendien suggereren we dat een focus op het expliciteren van de doelstellingen van beleidsmaatregelen kan helpen om belangrijke onderzoeksethische normen te waarborgen en tegelijkertijd cultureel imperialisme te voorkomen. Tenslotte stellen we dat het belangrijk is om te evalueren of en zo ja, wat de ontwikkeling en het gebruik van GDT onderscheidt van andere biotechnologieën en gebiedsdekkende interventies, en welke beleidsmaatregelen gerechtvaardigd zijn in het licht van zulke verschillen.

In **hoofdstuk 5** worden de ethische uitdagingen die GDT met zich meebrengen weergegeven op een manier die tot de verbeelding spreekt en die een breder publiek aanspreekt dan academische artikelen: door middel van foto's. Waar filosofische vragen vaak in geschreven teksten worden gesteld en geanalyseerd, kunnen foto's een meer toegankelijke en intuïtieve manier zijn om aan te zetten tot nadenken over de impact die opkomende technologieën kunnen hebben op ons leven en de wereld om ons heen. Op die manier dragen deze foto's bij aan het publieke bewustzijn en het debat over GDT.

Deel II: Ethische Landschapsarchitectuur – Evaluatie van de verantwoorde ontwikkeling en beleid van gene drive technologieën

Het tweede deel van dit proefschrift betreft wat metaforisch 'ethische landschapsarchitectuur' zou kunnen worden genoemd. In dit deel wordt geëvalueerd hoe het ethische landschap ontworpen of beïnvloed zou moeten worden, oftewel of en hoe GDT op een ethisch verantwoorde manier kunnen worden ontwikkeld en bestuurd. Daarbij worden drie specifieke ethische vragen en zorgen met betrekking tot de ontwikkeling en het beleid van GDT nader geëvalueerd.

Hoofdstuk 6 analyseert de morele toelaatbaarheid van het gebruik van GDT om opzettelijk muggen uit te roeien of te veranderen om de ziektelast van malaria te verlichten. Een belangrijk punt bij het bepalen van de morele toelaatbaarheid van het gebruik van GDT betreft de vraag hoe de inherente waarde en belangen van individuele mensen, niet-menselijke dieren en het milieu tegen elkaar moeten worden afgewogen. In dit kader is betoogd dat het tijd is voor een herevaluatie van bestaande overtuigingen dat de mens superieur zou zijn aan de niet-menselijke natuur en dat de inherente waarde van niet-menselijke organismen ook meegewogen zou moeten worden in een analyse van de morele toelaatbaarheid van GDT. Dit hoofdstuk gaat in op deze zorgen door te evalueren of de inherente waarde van individuele muggen reden kan zijn om af te zien van het gebruik van GDT. Eerst schetsen we verschillende perspectieven op welke organismen er moreel toe doen op basis van hun eigen inherente waarde. Omwille van het argument nemen we het meest omvattende perspectief op welke organismen inherente waarde hebben: een biocentrisch perspectief dat alle levensvormen dezelfde inherente waarde toekent. Vervolgens onderzoeken we hoe conflicterende verplichtingen jegens verschillende organismen vanuit dit perspectief geprioriteerd zouden moeten worden en passen dit toe op de context van malariabestrijding met GDT. Onze ethische analyse laat zien dat het principe van zelfverdediging van toepassing is op deze context, waardoor de prima facie bezwaren die een biocentrist tegen het gebruik van GDT zou hebben teniet worden gedaan. Dit brengt ons tot de conclusie dat, zolang aan bepaalde voorwaarden wordt voldaan, deze bezwaren geen doorslaggevende argumenten vormen tegen de inzet van GDT om de ziektelast van malaria te verlichten.

Hoofdstuk 7 evalueert het gebruik van 'ethische licenties' in de context van GDT en andere biotechnologieën. Octrooien zijn 'exclusiviteitsrechten' die kunnen worden gebruikt om privaat bestuur tot stand te brengen door te specificeren wie een licentie mag krijgen en onder welke voorwaarden. In de context van GDT-onderzoek heeft onderzoeker Kevin Esvelt voorgesteld octrooien op GDT te gebruiken om te voorkomen dat anderen deze technologie gebruiken zonder hun onderzoeksplannen en de bijbehorende veiligheids- en ethische kwesties openbaar te maken. Wij betogen dat, hoewel het prijzenswaardig is dat octrooihouders in hun licentieovereenkomsten een maatschappelijk verantwoorde aanpak nastreven, het gebruik van eigendomsrechten op deze manier procedurele rechtvaardigheidsproblemen oplevert. Fundamentele technologieën zoals CRISPR (Clustered Regularly Interspaced Palindromic Repeats) en GDT roepen vragen op over wat een 'maatschappelijk verantwoord' of 'ethisch' gebruik van deze technologieën zou inhouden. Dergelijk waardenpluralisme levert een legitimiteitsprobleem op: wie zou hierover mogen beslissen en onder welke voorwaarden? Wij stellen dat ethische licenties een breed debat moeten oproepen over de vraag of en wanneer deze benamingen van toepassing zijn, in plaats van het uitsluitend aan de octrooihouder over te laten om dit te bepalen. Een dergelijk proces zou op zijn minst een bredere groep belanghebbenden dan alleen de octrooihouder in staat moeten stellen om inzicht en invloed te hebben op de voorwaarden van de licentie die het aanvaardbare gebruik van de technologie bepalen. Meer specifiek stellen wij voor dat een platform van belanghebbenden uit de CRISPR of GDT-gemeenschap een modellicentie zou kunnen formuleren, inclusief overwegingen betreffende ethisch gebruik.

Ten slotte analyseert **hoofdstuk 8** de definitie en afbakening van de 'gemeenschap' in de context van veldproeven met gene drive organismen. Een belangrijk discussiepunt rondom deze veldproeven betreft wie moet worden geïnformeerd, geraadpleegd en betrokken bij de besluitvorming over het ontwerp en de uitvoering hiervan. In het algemeen wordt gesteld dat vooral leden van de gemeenschap betrokken zouden moeten worden bij deze besluitvorming. Toch bestaat er onenigheid en onduidelijkheid over hoe deze 'gemeenschap' moet worden gedefinieerd en afgebakend. Wij evalueren dit 'grensprobleem': het probleem van het afbakenen van de grenzen van in- en exclusie bij (GDT) *community engagement*. Wij stellen dat het belangrijk is om te definiëren en af te bakenen wie de gemeenschap omvat omdat dit noodzakelijk is voor het ontwerp en de evaluatie van effectieve en rechtvaardige gemeenschapsinterventies. Hiernaast kan dit helpen om ontevredenheid, verlies van vertrouwen en conflicten tussen verschillende betrokken partijen te voorkomen. Vervolgens tonen wij aan dat in het debat over GDT verschillende definities van gemeenschap door elkaar heen worden gebruikt, en pleiten wij voor het onderscheiden van geografische, getroffen, culturele en politieke gemeenschappen. Ten slotte stellen wij een eerste leidraad voor om te bepalen wie (niet) betrokken moet worden bij de besluitvorming over GDT-veldproeven. We stellen dat de definitie en afbakening van de gemeenschap moet afhangen van de redenen om hen te betrekken en dat de kenmerken van de gemeenschap zelf een leidraad kunnen zijn voor het ontwerpen van strategieën voor *community engagement*.

Deel III: Algemene discussie

Het derde deel van dit proefschrift bevat een algemene bespreking van de belangrijkste bevindingen. **Hoofdstuk 9** beantwoordt de onderzoeksvragen van dit proefschrift en plaatst de bevindingen in een breder perspectief. Ten eerste bespreek ik de ethische uitdagingen van GDT. Ik betoog dat eerdere discussies over *genome editing* technologieën onderstrepen dat het essentieel is dat de ethische evaluatie van GDT situationeel is ingebed, proactief en interdisciplinair wordt uitgevoerd, en een breed scala aan ethische argumenten omvat, waaronder (niet-consequentialistische) overwegingen met betrekking tot dier- en milieu-ethiek. Hierna identificeer en bespreek ik een reeks inhoudelijke en procedurele ethische uitdagingen van GDT. Ten tweede evalueer ik deze ethische uitdagingen en doe ik op basis van deze evaluatie aanbevelingen voor de verantwoorde ontwikkeling en

bestuur van GDT. Deze aanbevelingen betreffen de manier waarop de voordelen, risico's en onzekerheid van GDT zouden moeten worden benaderd, de voorwaarden voor de morele toelaatbaarheid van een technofix, de rol die de mens in de natuur zou moeten hebben, de doelen van *community* en *stakeholder engagement*, en welke beleidsmaatregelen er zouden moeten zijn om beslissingen over GDT te nemen. Ten slotte reflecteer ik op de inzichten die de resultaten van dit proefschrift opleveren voor ethisch parallel onderzoek als benadering voor vroegtijdige ethische begeleiding van nieuwe en opkomende technologieën meer in het algemeen. Ik betoog dat de vroege ethische begeleiding van nieuwe en opkomende technologieën niet alleen een normatieve evaluatie van verschillende standpunten en argumenten vereist, maar ook een conceptuele analyse van de belangrijkste termen. Bovendien stel ik dat de vroegtijdige ethische begeleiding van nieuwe en opkomende technologieën zoveel mogelijk concrete morele verplichtingen moet specificeren. Ten slotte is het belangrijk in gedachten te houden dat politieke deliberatie en besluitvorming noodzakelijk zijn om tot uiteindelijke beslissingen over de inzet van nieuwe en opkomende technologieën te komen. Dit laatste hoofdstuk sluit af met een overzicht van belangrijke aanbevelingen voor onderzoekers en beleidsmakers op het gebied van GDT.

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Curriculum vitae

Nienke de Graeff was born on the 24th of January 1989 in Utrecht, the Netherlands. After graduating from high school (Christelijk Gymnasium Utrecht) in 2007, she spent a year working, learning Spanish, and travelling in South America. In 2008, she commenced her studies in Liberal Arts & Sciences at University College Maastricht, during which she spent a semester abroad at the Universidad San Francisco de Quito in Ecuador. In her bachelor thesis 'Requests for euthanasia by dementia patients – a killing dilemma', Nienke investigated the medical ethical issues associated with euthanasia requests by dementia patients. She graduated *cum laude* and obtained the 'top 3% award' from Maastricht University in 2011. Subsequently, she started the medical master SUMMA (Selective Utrecht Medical Master), during which she conducted (extracurricular) clinical and laboratory research in the field of pediatrics. After graduating in 2015, she worked as a resident at the Intensive Care Unit at Ziekenhuis Gelderse Vallei in Ede. This work further sparked her interest in ethics, and she decided to go back to university, pursuing a pre-master and master's in Applied Ethics (*cum laude*) at Utrecht University from 2017 onwards. In December of that year, she started her PhD on the ethics of gene drive technologies at the department of Medical Humanities of the UMC Utrecht. She was supervised by prof. dr. Annelien Bredenoord and dr. Karin Jongsma. Next to her research, Nienke taught classes related to medical humanities, ethics and philosophy of science to (bio)medical students. She was a member of the Reproductive Ethics Committee at the UMC Utrecht, the Postgraduate Student Committee of the Institute for Medical Ethics in the United Kingdom, the guidance committee for nuclear transfer for mitochondrial disease at UZ Gent and the ZonMW user committee on spermatogonial stem cell transplantation in infertile childhood cancer survivors. In 2019, Nienke obtained a grant from the Girard de Mielet van Coehoorn Stichting for a three-month research visit to the Church group at the Genetics department of Harvard Medical School. In 2020, she received the 'EACME Paul Schotsman Prize' for young talented scholars. In the last phase of her PhD, Nienke conducted a postdoctoral research project commissioned by the Netherlands Commission on Genetic Modification (COGEM) in which she unraveled the conceptual and normative complexity of the terms 'nature' and '(un)naturalness' in the context of genetic modification. Moreover, Nienke leads the ethics workpackage of a ZonMW-funded project on stem-cell derived embryo models called gastruloids. After the defense of this thesis, Nienke will continue her work on the ethics of biotechnology as an assistant professor at the department of Ethics and Law at Leiden University Medical Center.

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