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RESEARCH ARTICLE

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Anomaly handling and the politics of gene drives

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ABSTRACT

Decisions about the development and use of gene drives are framing broader debates about the need for fundamental changes to biotechnology regulatory systems. We summarize this debate and describe how gene drives are being constructed as potential anomalies within the regulatory landscape. Drawing on literature from Science and Technology Studies and other fields, we outline a broad set of anomaly-handling strategies and provide examples from current gene drive debates. While often couched in technical terms, decisions about how to address anomalies are also decisions about whether to strengthen or weaken different forms of governance. By exploring the different ways that anomalies are constructed and handled, we highlight the active role that anomalies play within a changing governance system and invite a more nuanced examination of the multifarious goals these strategies serve.

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Introduction: gene drives as technical, policy, and political anomalies

In July 2015, the National Academies of Sciences, Engineering, and Medicine (NASEM) held their first public meeting of the Committee on Gene Drive Research in Non-Human Organisms (2015). The study was catalyzed in part by several papers describing 'gene drives': mechanisms to instantiate the spread of genetic modifications (GMs) throughout a population of sexually reproducing organisms with a much greater efficiency than normal inheritance (Esvelt et al. 2014; DiCarlo et al. 2015; Gantz and Bier 2015). The Committee met under agreement that such gene drive research and future applications may pose challenges to existing regulatory and oversight systems. Gene drives, in other words, were considered potential *anomalies* within these systems: things that deviated from what is standard, normal, or expected.

At the first meeting, the four organizations that funded the NASEM Committee, and thus set its statement of work, were given time to present the reasons they believed this Committee was needed. The following statements showcase the funders' competing

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priorities, visions of society, and understandings of the roles gene drives might play in realizing those visions and priorities.

The National Institutes of Health (NIH) and the Foundation for the National Institutes of Health asked the committee to focus on what needed to change within the current governance system so that the advancement of science could proceed:

> At the end of the day, the NIH's goal with this or any emerging technology which we spend time thinking about – or encouraging others to spend time thinking about – is really making sure we're supporting the best science to advance human health and that we're doing so under the highest ethical standards and approaches. (Wolinetz 2015)

'We feel very strongly that gene drive research has exceptional potential for adding to our arsenal of tools to control vector borne diseases' (James 2015). The Gates Foundation also invoked public health, but added humanitarian goals and spoke about how gene drives could offer strategies for addressing persistent challenges like malaria (Randazzo 2015). The Defense Advanced Research Projects Agency (DARPA), while funding this study, conveyed that deliberative processes like this could move too slowly to address security concerns, stating flatly that

> we may not have the time in this case to actually wait for, and make calls for, certain scientific actions and communities to deliberate. We may actually need to be working on technology solutions right now. And the alacrity of our [DARPA] institution is here to do that. (Wattendorf 2015)

The Committee members actively pushed back at these framings, pointing out how 'the tone of the statement of task [drawn up by the funders] presumes a certain level of technological development of gene drives is inevitable' (NASEM 2015). This concern has been matched by others who see gene drives as a step too far, too fast (CGS and FoE 2015).

The groups, and the framings they support, are vying to determine who gets to set the agenda (Baumgartner and Jones 2009), decide what is and is not discussed (Bachrach and Baratz 1962), and therefore settle what types of knowledge, technology, and society we pursue (Jasanoff and Kim 2015). While the funders' initial framings, which prioritized continued innovation, helped define the scope of work, the final report of the Committee prioritized precaution and responsible innovation (Kaebnick et al. 2016; NASEM 2016).

This push and pull between different ways of framing the content, purpose, and desirable direction of science and innovation is common in discourse around emerging technology. When it comes time to argue for specific regulatory changes, the discussion often becomes more nuanced and highly technical in nature. These technical discussions, however, are just as much debates about wider social issues.

We argue that debates about what a gene drive is, and how it fits within a regulatory system, are also debates about whether the regulatory system can be maintained or needs to be overturned. Gene drives, we argue, are constructed by different actors as potential anomalies to existing regulations in order to achieve certain social and political goals. Deciding whether a gene drive is an anomaly, and what strategy should be used to handle that anomaly, depends on which actors are involved and whether their goals and preferred way of framing a problem align with the current regulatory framework's dominant framing. In other words, an actor's definition of a gene drive is co-produced with the type of regulatory system that the actor believes in (Jasanoff 2004).

After a brief background on the current regulatory environment, we outline a set of anomaly-handling strategies that have been or might be used to either further cement or undermine the established ordering of regulatory systems. We conduct this analysis with a focus on the American regulatory system and its linkages to international systems.

Shifts in the biotechnology regulatory landscape

There are many signs that the next few years may present opportunities to shift the biotechnology regulatory system. There is increasing attention to the economic potential of biotechnology (OECD 2009; US White House 2012). Genetic engineering technologies, including genome editing tools such as CRISPR[1] (which underlies current gene drive research), are being used or proposed for a wide range of headline-grabbing applications (e.g. Baltimore et al. 2015; Charo and Greely 2015). Gene drives are often presented as extreme cases among a broader suite of developments, raising questions about the sufficiency of current regulations to handle the scope, scale, and diversity of biotechnology applications and their developers (Webber, Raghu, and Edwards 2015; Thomas 2016; Latham 2017).

When the US Coordinated Framework for Regulation of Biotechnology was developed in 1986, it included a set of tenets intended to ensure public safety without overburdening the fledgling biotechnology industry with regulation. These tenets include (1) focusing regulation on the products of GM techniques rather than the process itself; (2) grounding regulation in verifiable scientific risks; and (3) placing GM products on a continuum with existing products such that existing statutes are sufficient to review the products (Marden 2003, 738). These tenets look different from those of other regulatory environments, such as the European Union, which focus more on the process, creating rules and authorities specific to GM (Jasanoff 2005a).

One major sign of potential shifts in the regulatory systems is the comprehensive review of the framework conducted by the President's National Science and Technology Council (NSTC) from 2015 to 2017. This review, recently published (Biotechnology WG 2017), is the first major update since 1992. Gene drives were not included in the set of hypothetical case studies put forward by NSTC in the first stage of public consultations, but they were raised in public comments as examples of technologies that may not fit neatly within the current framework. For example, it was unclear whether gene drives in rodents would be regulated as animal drugs, or whether the animal itself would be regulated as a pesticide (Carter 2015). The NSTC also commissioned a coupled forecasting study conducted by the NASEM Committee on *Future Biotechnology Products and Opportunities to Enhance the Biotechnology Regulatory System*. Gene drives featured prominently in the study's report (NASEM 2017).

Another notable sign of increasing attention to changes needed in the regulatory and policy systems is the development of the concept of Dual Use Research of Concern (DURC).[2] A series of experiments involving mousepox, botulinum toxin, and influenza in the early 2000s ignited debate about security concerns that arise from conducting research. In response, the US government rolled out a set of policies to provide additional oversight for research deemed to have potential security concerns (USG 2012, 2014). Application of these policies, however, is currently limited to a small set of experiments conducted on a limited number of organisms and funded by the US government. Nevertheless, these policies put a spotlight on the need for oversight in earlier stages of research

and development. Gene drive research has been raised as an example of research not currently covered under these policies, even though this research could have widespread deleterious effects (Oye et al. 2014).

Some of the most contentious international debates about regulatory frameworks have surrounded the Convention on Biological Diversity (CBD). At its October 2010 meeting, discussions of synthetic biology risks led to the appointment of an Ad Hoc Technical Working Group (CBD 2010). At this working group's December 2016 meeting, non-governmental organizations (NGOs) highlighted gene drives as technologies raising serious challenges to the access and benefits sharing and biosafety goals of the convention and its protocols. The idea of a moratorium on gene drives found hold at the meeting, though the final agreement instead urged better risk assessment and caution for field tests (Callaway 2016). While the US is not signatory to the CBD, decisions at these meetings will become policy in many countries with whom the US trades.

Meanwhile, disease outbreaks such as Ebola and Zika are raising public consciousness about biological threats, and accidents at biological laboratories are undermining confidence in our ability to manage risks in research (Palmer, Fukuyama, and Relman 2015). The US intelligence community has recently elevated the security profile of genome editing, listing it as a potential weapon of mass destruction threat alongside chemical weapons in Syria and Iranian nuclear developments, rather than a threat within a range of other technical innovation spaces like artificial intelligence and the internet of things (Clapper 2016). This statement puzzled practitioners and policymakers alike (Regalado 2016). Internationally, conversations related to misuse have centered on the Biological Weapons Convention (BWC), which held its eighth five-year review conference in November 2016. While the review was largely characterized as a failure, an InterAcademy Partnership report on trends in science and technology relevant to the BWC highlighted how advances are degrading barriers to misuse and discussed gene drives as an example of a novel targeting agent (InterAcademy Panel et al. 2016; Wood 2016).

These events position the regulatory system for reconsideration and reconfiguration, and gene drives are often presented as extreme cases of the current system's failure. This is a moment of policy change where the definitions of the issues at hand are up for revision (Baumgartner and Jones 2009). Also up for contention are decisions about the ontology of gene drives (i.e. what is the nature of gene drives), who should work with them, and for what purposes. By outlining strategies to construct and handle gene drives as anomalies within discussions concerning regulatory systems, we invite more nuanced consideration of the multifarious goals these strategies serve. In the absence of such considerations, changes to regulatory systems are likely to be enacted reactively and within a narrow framing.

Gene drives as potential anomalies

Gene drives are an area of development that might disrupt established ways of regulating biotechnology. That is, a gene drive may be an ***anomaly*** within the regulatory system. We are using 'anomaly' in Mary Douglas' (1966, 38) sense of 'an element that does not fit a given set or series'. Her work on anomalies could be considered a starting point for this paper, as she focused on how decisions were made to construct and resolve anomalies related to pollution and taboo, and how those decisions were intimately related to the maintenance of social orderings.

We contend that whether gene drives represent an anomaly within current regulatory and oversight systems depends on who is making the argument, with what evidence, and within which context. To build a case that gene drives do or do not fit within current regulations, individuals and organizations must answer questions such as: how do we define gene drives? How do they fit within current regulatory classifications? Are there alternative ways that they could be defined and classified? This process of creating definitions and arguing for their (in)compatibility within the regulatory system is one of anomaly construction and handling.

For example, in creating the NASEM report's gene drive definition, the Committee on Gene Drive Research decided to highlight two attributes of gene drives that it saw as anomalies within the current regulatory framework: 'their intentional spread and the potential irreversibility of their environmental effects' (2016, 7). The Committee uses these attributes to argue, among other things, that current forms of risk assessment are inadequate, that a new form – ecological risk assessment – would be better able to accommodate them as anomalies, and that, on the whole, their '[i]ntentional spread challenges current governing systems for biotechnology' (149).

Upon constructing a gene drive as an anomaly within regulatory systems, different strategies are employed to address that anomalous status. While often couched in technical terms, decisions about how to address an anomaly also are decisions about strengthening or weakening different forms of governance. We look at several anomaly-handling strategies in turn below and demonstrate how choosing a particular strategy in a particular situation is both a political and a technical action. This analysis highlights the powerful roles anomalies play within a changing governance system.

Anomaly-handling strategies

We are not the first to consider the role anomalies play in changing the way we organize the world. Many scholars in Science and Technology Studies (STS) have examined how social, cultural, political, and economic orders are 'co-produced' (Jasanoff 2004) with technical and scientific orders, and have examined how anomalies challenge those orders. Kuhn ([1964] 1996) focused on the role of anomalies in the production of scientific revolutions. Bowker and Star (1999) used anomalies to study the composition, solidification of, and challenges to classification systems. Latour (1993) examined the role of 'hybrid' crossovers between human and nonhuman. Haraway's (1991) cyborgs, Law's (1991) and Jasanoff's (2005b) monsters, and Rayner's (2012) 'uncomfortable knowledge' also explore anomaly construction and its relationship to established orders. Brian Rappert (2001, 2005) explicitly discusses anomalies and a range of strategies employed to address them.

Outside of STS, John Dewey's pragmatist philosophy focused on the construction and resolution of a 'problematic situation' through its transformation, such that it no longer presents a point of tension. This is perhaps the most general description of anomaly resolution (Dewey 1903). Lakatos (1976) examined anomaly resolution within mathematics, which Bloor (1978) showed to be much more widely applicable. Anthropologist Mary Douglas broke down the perceived differences between primitive and modern cultures by studying how both employ similar strategies to address the anomaly of 'dirt', which is 'matter out of place' (1966, 36). In calling out something as an anomaly, she argued, we are also defining the boundary of the set from which it deviates.

Below we outline a set of strategies that organizations use for handling anomalies. We examine how these strategies manifest within discussions related to public institutions such as regulatory systems and issues like gene drives. We divide these anomaly-handling strategies into three major categories, depending on the degree to which they threaten the established ordering within a regulatory system. First are strategies that argue gene drives are not anomalies at all. We then turn to strategies that acknowledge gene drives as anomalies but argue that the current regulatory system can adequately accommodate them. Finally, we outline strategies that acknowledge gene drives as anomalies and argue that the current system cannot accommodate them. Like the authors before us, we intend for this to be an indicative list, not an exhaustive one (Figure 1).

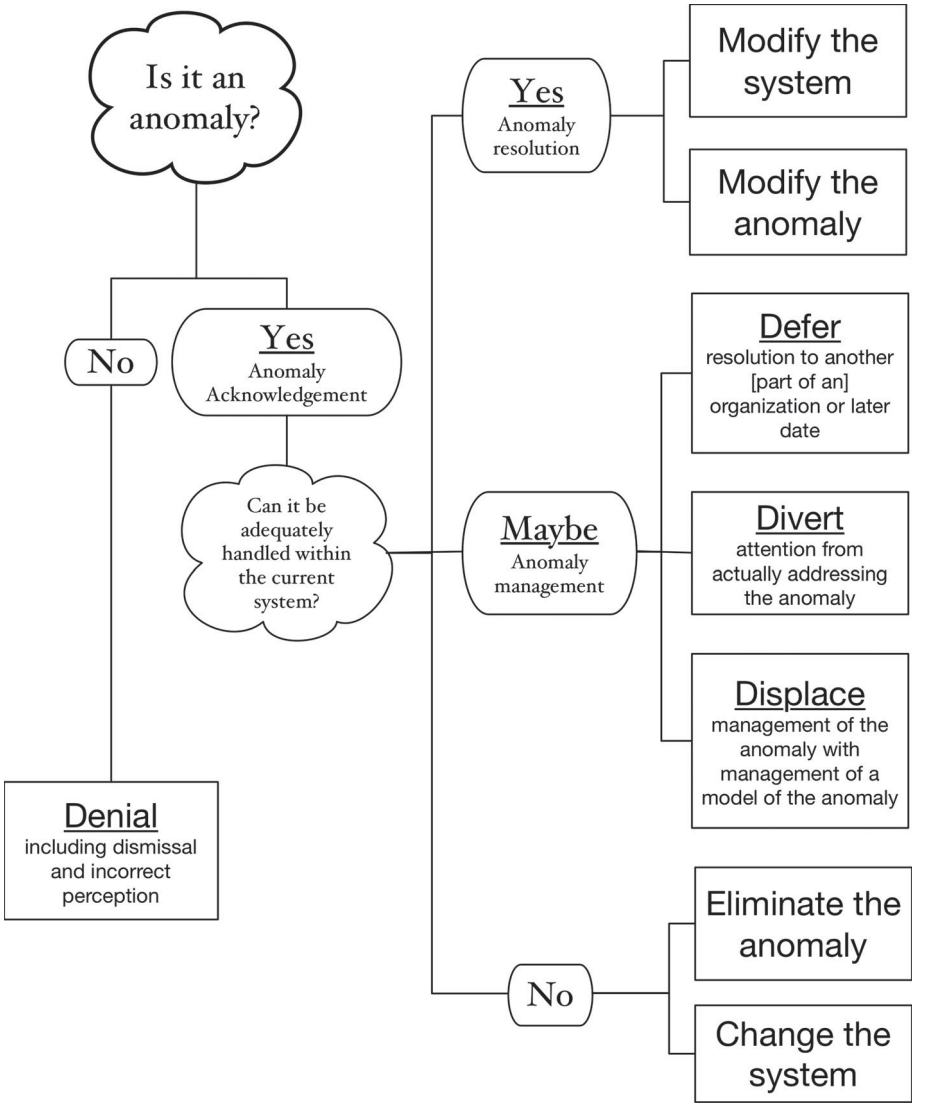

Figure 1. Anomaly-handling strategies.

Strategies that argue gene drives are not anomalies

Denial (including dismissal and incorrect perception)

The simplest anomaly-handling strategy is to say, for a particular purpose, that an anomaly does not actually exist (Douglas 1966, 36). For gene drives, this could take the form of a broad denial that gene drives represent anything new or that they exist at all. For example, some have said that 'gene drives are natural and already widespread in wild populations' (Spradling 2015). Another form of denial is what Rayner (2012, 116–118) calls dismissal: asserting that gene drives do not exist in any way that is meaningful to the regulatory system. Another argument is that the potential anomaly is perceived in the wrong way. Correctly perceived, it is not an anomaly, but a normal example that is covered by the classification system, what Lakatos (1976, 30–33) called 'monster-adjustment'. However, there is a political cost to denial. If an individual or organization ignores a potential anomaly that others think exists, that individual or organization risks losing credibility (Douglas 1966, 38–39; Lakatos 1976, 42–43; Rappert 2001, 235; Rayner 2012, 113–116).

In practice, we can observe both denials of gene drives' existence and dismissals. For example, some have pointed to experiments demonstrating that wild populations may quickly evolve resistance to argue that defining attributes of gene drives – persistence and propagation through an entire population – are moot and therefore not things that the regulatory system must deal with (Callaway 2017; Unckless, Clark, and Messer 2017). Similarly, if a gene drive is argued to be only a new process for producing the same products (i.e. an altered phenotype), current regulations directed at products, not processes, would deny that gene drives are an entity that needs special consideration.

Anomaly resolution: strategies that accept gene drives as anomalous but adequately resolved by the existing system

The next two strategies focus on situations where gene drives are ascribed anomalous status, but the anomaly is resolved fully. If there is acceptance that gene drives physically exist with attributes that make them anomalous within the regulatory system, then decisions must be made on how they are to be handled. These strategies are not always, or perhaps even often, explicitly chosen between. Institutions do a lot of thinking for us (Douglas 1986) and public institutions conform to culturally embedded ways of deciding what counts as credible knowledge to remain legitimate (Jasanoff 2005b, 265–289). In most cases, then, resolving anomalies through these strategies is simply about following the routine procedures of existing institutions.

Modify the regulatory system

One of the most common methods of handling an anomaly is to fit it into the existing system of classification by making minor modifications to that system. There are at least two ways these modifications might happen.

First, existing categories can be modified to either include or exclude a potential anomaly, what Lakatos calls exception-barring (1976, 24–30) and concept-stretching (83–87). This strategy is considered routine maintenance of classification systems of all types. One such classification system is the Australia Group, a multilateral

export control arrangement between states that maintains a list of biological and chemical items whose international trade is monitored due to perceived security implications. When a new item is developed or an item is newly deemed to be a security concern, the list is modified to accommodate it (e.g. Australia Group 2016; Fairchild et al. 2016).

Second, a regulatory or policy system might change the types of knowledge that are deemed necessary to making regulatory decisions. The NASEM (2016, 8) report constructs gene drives as regulatory anomalies by arguing that their attributes – their intentional spread and the potential irreversibility of their environmental effects – challenge the legislation that governs how the US generates knowledge about environmental risk, the National Environmental Policy Act (NEPA). NEPA relies on 'environmental assessments' and 'environmental impact statements', which the report argues and 'are inappropriate tools to characterize the risks of gene-drive modified organisms' (126). Instead, the Committee suggests a strategy of modifying regulations to require ecological risk assessments, which are already used in other areas such as the control of toxic substances and Superfund sites (116).[3]

Modify the anomaly

It is also possible to modify the anomaly rather than the classification system (Smits 2006). Many scientists working on gene drives are also developing technical modifications to address some of the ways these drives might be perceived as regulatory anomalies. These efforts include work on molecular strategies for biocontainment (Esvelt et al. 2014; Akbari et al. 2015), reversal and immunization drives (DiCarlo et al. 2015; Champer, Buchman, and Akbari 2016), and drives that can be limited to a certain number of generations (Min et al. 2017a, 2017b). This research agenda has received a notable boost with the development of the DARPA Safe Genes Program. One goal of these approaches is to accommodate a regulatory process built on stepwise contained field trials by embedding containment steps within the technology itself.

Why choose a technical modification to meet regulatory requirements as an anomaly-handling strategy? It can propel discussions about applications by moving discussion away from a strategy of preventing development of the technology. Technical modifications are often presented as concrete answers to intractable social problems and used to close down debate about those problems. Such modifications also make the technology look less dangerous, thus more likely to be developed and used.

Modify the regulatory system and the anomaly

In practice, technology modification happens along with regulatory or policy system modification (Smits 2006, 501). Such joint modification may occur when new requirements apply to an area of research or technology development. In both the international Genetically Engineered Machines student competition policies (iGEM 2017) and the Association for Biosafety and Biosecurity (ABSA) biosafety training, gene drives are presented as special cases, or anomalies, within the current policies that govern what work is allowed to move forward. These gene drive policies draw lines around what research is permissible at different stages, which impacts both what research is done and how research must be framed to be acceptable to the governing bodies.

Anomaly management: strategies that accept gene drives as anomalous, not adequately resolved by the system, but still governable

The above two strategies focus on acceptance of an anomaly's status and changes that bring the anomaly in line with an existing system. There are many anomalies, however, that are not so easily resolved, and organizations have worked out several ways that these too can be made non-threatening to the established ordering of knowledge and society. Any government or society will routinely employ these strategies to keep itself cohesive, because the problems these societies are trying to solve are 'wicked': intractable, multiply defined, nested, and persistent (Rittel and Webber 1973). These strategies are less about anomaly resolution and more about anomaly management.

Defer resolution of the anomaly to another (part of an) organization or to a later date

The first strategy we look at is deferral (Rappert 2001, 2005). Deferring an anomaly's resolution involves arguments that the anomaly is being discussed out of proper context. Deferring can also involve arguing that the anomaly is best resolved at a later date. While some often characterize this strategy as 'passing the buck', there can be legitimate reasons for it. For example, this strategy can allow for the time necessary to value the context-specificity of gene drive applications.

Deferral is currently a pervasive strategy in gene drive discussions. As Oye (2014, 11) says, 'the bottom line is that we need to move cautiously. Scientists need time to evaluate the risks and develop safeguards. Legislators need time to evaluate regulatory arrangements. And the public deserves time for an informed debate'. Moving cautiously involves preserving opportunities for deferral despite often severe pressure for a decision to be made quickly. By instituting measures like pre-registration for conducting gene drive research, or openly publishing grant proposals before research is initiated (Esvelt 2016, 2017a), deferral advocates hope that more time will allow for a broader set of discussions about how the work might best be governed.

Deferral is also seen in calls for resolving ambiguities around risk on a case-by-case basis, as stated in Recommendation 8-5 in the NASEM gene drive report: 'Relevant agencies and decision-making bodies will need to develop the capacity for robust assessment of a gene-drive modified organism's risks and uncertainties on a case-by-case basis that looks at the organism's intended function as well as the biological construct' (2016, 171). This strategy maintains a state of ambiguity over which agencies, or parts of agencies, have jurisdictional authority.

Divert attention from addressing the anomaly

Diversion is 'the organizational strategy of establishing a decoy activity that distracts attention from a subject or problem, thus ensuring that knowledge about it is not created or shared' (Rayner 2012, 118). This strategy is similar to Rappert's (2005, 236) strategy of deterrence. Those with the power to resolve anomalies will use diversion to prevent less powerful groups from unpacking a system's internal mechanisms of resolution.

An example of diversion can be observed in the position of social science expertise within major science and engineering projects. Social scientists are often put in less powerful positions that prevent them from questioning and expanding the methods by which

knowledge is produced in that project. At the same time, social scientists are often used to provide external legitimacy to organizations as token representatives of an often-critical community (Rabinow and Bennett 2012; Balmer et al. 2015).

A recent award by the Tata Trusts shows early signs of this type of diversion (Griffin 2016). The Tata Trusts issued $35 million to build research centers on 'active genetics' (a term that covers many of the same attributes that others have given to 'gene drives') at the University of California, San Diego, and an equivalent sum to support a complementary research enterprise in India. Noticeably missing from the description of the 'Society and Ethics' thrust (Griffin 2016), and from the project website at http://tigs.ucsd.edu/ as of October 2017, is any questioning of whether this type of work is a good idea at all, what might constitute responsible innovation in this case, and what expertise on the leadership team would best advance these questions. In a review outlining their vision for the research field, the main scientists involved provide only a superficial comment that '[w]e hope that this exciting journey will be charted in a judicious and ethical fashion' (Gantz and Bier 2015, 62).

Displace management of the anomaly by management of a model of the anomaly

Displacement is the 'process by which an object or activity, such as a computer model, designed to inform management of a real-world phenomenon, actually becomes the object of management' (Rayner 2012, 120). Many people are concerned about the impact of releasing a gene drive into the environment, and modeling might be used to understand possible effects before a release occurs (NASEM 2016, 119–123). There may be a tendency, however, to substitute modeling for sampling. Rayner (2012) notes how this happened when modeling the effects of policy decisions on water restoration in the Chesapeake Bay. The model was used instead of actual measurements to show that policy changes had significantly decreased pollution in the Bay, whereas measurements showed no discernible trend in water quality.

For gene drives, we may observe anomaly displacement through management of models related to their ecological effects. Models determining drive effectiveness and environmental effects are already valued in the gene drive research community (e.g. Unckless, Clark, and Messer 2017). An entire chapter of the NASEM gene drive report is dedicated to developing generalizable ecological risk assessment as a tool for policymakers, noting '[a]n essential component of the ecological risk assessment process is developing a model that accurately portrays the relationship between stressors and endpoints, known as a cause–effect model' (2016, 119 and Recommendation 6-1). Given the complexity and cost required for widespread and long-term empirical analysis of ecological effects, and the desire to determine these effects before release, model displacement will likely play a large role in making release decisions and in dictating how data about effects are gathered. Such a strategy has been shown to help prevent 'uncomfortable knowledge' (Rayner 2012, 120–122) that might undermine decisions about whether to release a drive.

Strategies that accept gene drives as anomalous but not adequately handled by the existing system

So far, all the strategies laid out have sought to maintain the established system of policies and regulations and accepted that the potential anomaly is here to stay. But anomalies can also be handled so as to demand more drastic action.

Eliminate the anomaly

Smits (2006, 500) and Douglas (1966, 40) point out how anomalies that are seen as clear aberrations to a way of ordering often lead to calls for the complete elimination of the anomaly. This kind of anomaly-handling strategy often occurs in the form of a moratorium, and it is often used by those who place a priority on clear lines over which society should not cross. That nuclear weapons still exist, despite significant consensus that they should be eliminated, is one example of how difficult this strategy is to carry out in practice. This strategy can also have a temporal component, and in such cases, this strategy resembles deferral.

Moratoria like those used in the 1970s on genetic engineering, and those on gain-of-function work and human germline engineering in the last few years (Baltimore et al. 2015; CGS and FoE 2015) are examples of this strategy at work. Several moratoria have already been suggested for gene drive research (e.g. Kaebnick 2015; Callaway 2016; CSWGGD 2016a; Latham 2017).

This strategy can also tend toward deflection (Rappert 2005, 236). For example, a ban on biological weapons may deflect the focus of debate from a moral argument (is killing with disease bad?) to a technical one (how do we know when a disease is a weapon?).

Change the policy or regulatory system

Finally, when anomalies pile up, some might argue that the ordering or classification system as a whole is founded upon false premises and must be changed; what Lakatos (1976, 13–14) calls surrender. The main difference between this strategy and one that modifies the regulatory system is the degree to which changes overturn foundational assumptions about how knowledge, technology, and society should be ordered.

Current biosafety standards and oversight arose from such a situation. In the 1970s, as techniques for genetic engineering were being developed, many worried that these techniques were anomalies within regulatory, ethical, and other contexts (Wright 1994, 113–159). To proceed with research and development, the laboratory biosafety regulatory system was developed by creating government committees to review proposed projects, institutional committees to monitor research, and a tiered system of safety levels for experiments and laboratories. While this program was designed largely by scientists, it was overseen by the government and represented a major shift away from principles of scientific autonomy that had shaped many of the sciences since World War II.

If accidental gene drive releases were to occur and have severely deleterious effects, they might, for example, lead to much broader restructuring of concepts like academic freedom, the social contract for science, and the product versus process divide in different national regulatory systems, changes already long overdue (Evans and Valdivia 2012; Esvelt 2017b).

The politics of asserting and handling anomaly status

In this article, we have been exploring how regulatory systems order the things they govern. In this section, we show how anomaly handling depends on whether the organizations and people doing the handling want to stabilize or undermine these existing ways of ordering. We analyze several of the strategies that are currently being deployed around gene drives within the regulatory context, drawing out the reasons given by those who are employing the strategy.

It is important to remember that anomalies, and thus strategies to handle them, only exist if there is already an ordering system in place. In other words, anomalies are context-specific to a particular way of ordering the world. Moreover, there are many ways of ordering the world. An anomaly within one ordering system may be non-anomalous within another. Anomaly-handling strategies come into play, therefore, when different systems of ordering come into conflict.

Elimination of the anomaly

First, we turn to calls for the ***elimination of the anomaly***. Perhaps the strongest example to date of this strategy is the *Common Call for a Global Moratorium on Genetically-Engineered Gene Drives*, a statement prepared by the Civil Society Working Group on Gene Drives (CSWGGD 2016a) in advance of the 2016 Conference of the Parties to the UN Convention on Biological Diversity. Signatories include 157 non-governmental organizations from across the world.

What makes a moratorium the only reasonable strategy to this group? In another document produced by the CSWGGD (2016b), the group discusses how gene drives give 'technicians the ability to intervene in evolution, to engineer the fate of an entire species, to dramatically modify ecosystems, and to unleash large-scale environmental changes, *in ways never thought possible before*' (emphasis added). Gene drives, to this group, undermine a wide array of existing orders, both natural and social, including: 'biodiversity, national sovereignty, peace and food security'. The primary regulatory system in play here is the UN CBD, and its objectives are to uphold those orderings of nature and society that this group claims gene drives threaten: 'The objectives of this Convention … are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources' (CBD 1992). An argument to eliminate the anomaly is an argument to maintain the regulatory system and the other orderings valued by these groups.

Developing this technology, they argue, involves crossing a moral and ethical threshold and is 'in direct contradiction to the moral purpose of conservation organizations', some of which are supporting initial development of gene drive capabilities (CSWGGD 2016a). They are also concerned about potential use by the military and that 'current regulatory schemes are not capable of evaluating and governing this new technology'. This argument of new technologies crossing a line too far is a familiar strategy employed both in earlier developments in biotechnology and in other technologies (Douglas 1966).

One problem with this strategy, visible in calls for moratoria, is that it can constrain public and ethical deliberation to a single stage in the innovation cycle, rather than encourage a continuous process. This strategy suggests that questions are answerable through one-off consideration, rather than through continued engagement. Even after scientists call for new processes to support ongoing public debate, the debate often ends if and when moratoria are lifted (Jasanoff, Hurlbut, and Saha 2015).

Anomaly resolution through system modification

Next, we examine an instance of ***anomaly resolution through system modification***. As discussed earlier, the National Academies report on *Gene Drives on the Horizon* pushed

to incorporate ecological risk assessment into a regulatory structure for gene drives (NASEM 2016, 128). This was not the only system modification that the report suggested, however. The committee recommended a series of modifications that they deemed necessary to manage gene drives' two anomalous attributes: intentional spread and the potential irreversibility of their environmental effects (149–150).

What were the modifications? In addition to incorporating ecological risk assessment, the Committee also recommended revising laboratory research oversight, particularly Institutional Biosafety Committees (IBCs). The report stated that 'the novel characteristics of gene drives, capacity issues, and an absence of clearly defined guidelines for gene drive research' meant that 'current IBCs may not have the expertise or resources to evaluate the biosafety of gene drives effectively', and that 'IBCs are also not equipped to examine biosecurity or willful misuse issues' (NASEM 2016, 170). Recommendation 8-2, however, argued that IBCs are still a legitimate governance tool in this space, with modification: '[F]unding agencies and research institutions should take responsibility to ensure the development of the necessary expertise to assess safety within Institutional Biosafety Committees and their equivalents' (170).

Why were they making these recommendations? One answer comes from an article that a subset of the authors published in *Science* shortly after the NASEM report came out (Kaebnick et al. 2016). In it, the authors call for counteracting a long-standing desire in science to get an 'innovation thrill'. This term originally referred to J. Robert Oppenheimer's comments before Congress on why he and his team developed the atomic bomb: 'When you see something that is technically sweet, you go ahead and do it and you argue about what to do about it only after you have had your technical success' (771). At least to this subset of the NASEM Committee, it is clear that gene drives would inevitably be used if their governance were left in the hands of scientists. To counteract the innovation thrill, the NASEM report put forward a nuanced argument for precaution and used gene drives' anomalous status as a reason to modify the governance system in ways that may curtail innovation for innovation's sake.

Anomaly resolution through anomaly modification

Last, we examine an instance of ***anomaly resolution through anomaly modification.*** This strategy of developing technical approaches to fit regulatory and policy goals, including safety, appears frequently in bioengineering (Isaacs et al. 2011; Mandell et al. 2015; Rovner et al. 2015), and is receiving significant attention within gene drive research and development. For example, a majority of scientists engaged in early gene drive development outlined a set of confinement strategies to be employed whenever gene drive work is conducted (Akbari et al. 2015). These strategies included separating the components required for genetic drive within a genome, performing experiments outside the habitable range of the organism, using a laboratory strain that cannot reproduce with wild organisms, and establishing more traditional physical barriers between organisms and the environment. These recommendations are already being adopted by most gene drive researchers (e.g. Hammond et al. 2016).

All of these strategies involve changing either the construct of a gene drive or the research practice that makes the construct a concern while doing experiments. Two examples of this strategy are work on 'daisy drive' systems designed to allow gene

drives to spread only at a local level, and on 'reversal' drive systems that overwrite previously released gene drives. These strategies negate the two primary attributes of gene drives that the NASEM report used to justify its recommendations on regulatory changes (Noble et al. 2016; Min et al. 2017a, 2017b). Daisy drive work has also been undertaken with a belief that 'ethical gene drive research and development must be guided by the communities and nations that depend on the potentially affected ecosystems' (Noble et al. 2016). Such guidance, however, 'becomes progressively more challenging as the size of the affected region increases'. The researchers' solution is 'a method of confining gene drive systems to local populations [to] greatly simplify community-directed development and deployment while also enabling safe field testing'. They hope this technical solution will allow for a more democratic decision process in local communities.

Anomaly modification is often a strategy employed to provide a technical solution to a social problem in an attempt to quell debate on those problems. However, in at least some of the current work on gene drives, this strategy may actually *enable more* debate by attempting to localize drives so they function within a particular geographic and democratic space, such as an island or a state.

Conclusion

Are gene drives anomalies within the current regulatory system, and if so, what should be done about them? Debate on this question continues. In this paper, we have laid out how answers to this question are tied to the context within which people decide whether gene drives are or are not anomalies and their visions of how the world should be ordered. We have outlined the broad set of anomaly-handling strategies that we have seen, or expect to see, for gene drives, and we have shown how these strategies are used to either undermine or support existing social and technical orderings.

Gene drives are already an active site of anomaly construction and handling, and we can expect this to continue in the coming years. In negotiating what gene drives are and should be, why we might want or not want them, and who has the power to decide the answers to these questions, we are also negotiating among different visions of the future. Anomaly handling is therefore inherently political, as these decisions reinforce whose visions, priorities, and interests are promoted. By unpacking the range of anomaly-handling strategies, we hope to have demonstrated how decisions on the anomalous nature of gene drives are also decisions on whether the current regulatory system is adequate, and for whom.

Arguments for the elimination of any research on gene drives or their countermeasures, for example, may also be arguments for an organizational structure that favors precaution, equity, and participatory processes. Decisions that finalize gene drives as anomalies to be resolved or managed within current regulatory systems strengthen those systems' way of ordering both the technical and the social world (such as determining who has the power to decide what attributes of gene drives are considered in governing their development or use). Similarly, decisions that finalize gene drives as inadequately governed within current regulations can lead to fundamental shifts in the regulatory system.

Large actively funded projects on gene drives that are likely to be sites of anomaly handling in the coming months and years include the work supported under the DARPA Safe

Gene program, the Target Malaria Project focused on Africa, and projects supported by the Tata Trusts, which is set up to share knowledge on gene drives between the US and India. The Foundation for the NIH has also recently catalyzed a consortium of funders of gene drive work motivated in part by an interest in addressing regulatory issues. Other groups are also attempting to develop capabilities.

Finally, the literature on anomaly handling spans several decades and topical areas. We expect that our advancements on this literature, examining gene drives and regulatory systems, will be relevant to many other areas of debate over maintaining and dismantling technical and social ordering systems.

Notes

1. CRISPR stands for 'Clustered Regularly Interspaced Short Palindromic Repeats'.
2. The US government's definition of DURC is

> life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. (see USG 2012, 2015)

3. According to the Committee,

> Examples of regulations that describe and require ecological risk assessment processes include the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Resource Conservation and Recovery Act (RCRA), and the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), more commonly called Superfund, and to Toxic Substances Control Act (TSCA). (NASEM 2016, 116)

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