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Economic issues to consider for gene drives

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ABSTRACT

We examine four economic issues regarding gene drive applications made possible by gene editing technologies. First, whether gene drives are self-sustaining or self-limiting will largely determine which types of organizations have incentives to develop and deploy gene drives and greatly influence their governance and regulation. Social factors will also play key roles, particularly public perceptions, with these perceptions co-determined with regulation and governance. Second, gene drive applications will generate unintended negative social impacts that will partially offset benefits. Third, economic surplus, the traditional measure of economic benefits, incompletely captures the welfare impacts of gene drive applications. Fourth, gene drives imply dynamic nonlinearities that make identifying economic equilibria and general policy recommendations challenging. The potentially substantial benefits, coupled with the technical, social, and economic uncertainties surrounding gene drives, suggest that a responsible course of action is to move forward while maintaining regulatory flexibility and conducting research to resolve key uncertainties.

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Introduction

Scientists involved in the development of new technologies, such as those who make gene drives possible, often work in wider academic and societal contexts that emphasize the advance of knowledge over the subsequent moral and welfare questions regarding the practical use of knowledge (Stilgoe, Owen, and Macnaghten 2013). Gene drives made possible by accurate gene editing (CRISPR-Cas9, TALEN, ZFN) are a potentially valuable new opportunity to make substantial improvements in the human condition globally (Esvelt et al. 2014; Hsu, Lander, and Zhang 2014). Several papers, including some in this special issue, describe the technical aspects of different gene editing methods and of different types of gene drives. In short, human-designed gene drives use gene editing to engineer individuals that upon release into a breeding population promote the prevalence

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of selected genes so that, for example, over many generations the population collapses or no longer vectors certain diseases. Proposed applications have focused broadly on pests (Esvelt et al. 2014), a focus continued here.

Eliminating or greatly reducing endemic diseases and parasites using gene drives could aid the economic development of tropical and sub-tropical regions (Gallup and Sachs 2001; Sachs and Malaney 2002; Esvelt et al. 2014). Endemic diseases and parasites impose large burdens on these regions, with many infected persons requiring long periods of treatment and convalescence, and suffering life-long losses of capacity and productivity (WHO 2014). Furthermore, travel, trade, and climate change will expand the ranges of many insect vectors and parasites, bringing these problems to new regions and to new populations (Hales et al. 2002; Patz et al. 2005).

By eliminating or effectively managing pests that reduce yields or crop quality, gene drives also offer the potential to enhance agricultural production at a time of growing global food needs (Tillman et al. 2011; Esvelt et al. 2014; Pardey et al. 2014). Maintaining and increasing agricultural productivity will continue to be difficult, as the effects of climate change have already been demonstrated (Lobell, Schlenker, and Costa-Roberts 2011, 2014; Mourtzinis et al. 2015). Increasing agricultural productivity could reduce resource use for food production, including land, energy, water, fertilizer, and pesticides. Increased productivity might also aid development in many nations by contributing to lower food prices, allowing economic resources to be used for other purposes, such as education and health care. Gene drives also offer the potential to reduce substantially the use of pesticides in crop and livestock systems by eliminating or managing pests genetically, thus reducing negative externalities from pesticide use (Florax, Travisi, and Nijkamp 2005). However, increased production efficiency may be translated into lower input costs per unit of production, which can make marginal or risky areas potentially more attractive for agricultural production. The long-term ecological impacts and effects on resource use and economic productivity of such expansion of production are hard to predict.

Gene drives also have the potential to make significant contributions in conservation (Esvelt et al. 2014). For example, they could be used to eliminate or manage populations of invasive species, which have disrupted managed and native ecosystems and have contributed to species extinctions. Some invasive species are agricultural pests, but many are not, yet nonetheless cause tremendous damage. Pimentel, Zuniga, and Morrison (2005) estimate annual losses from invasive species reach almost $120 billion in the US alone (also see Olson 2006 and Lovell and Stone 2005). Furthermore, as noted, travel, trade, and climate change will continue to increase the global spread of invasive species.

In the context of responsible innovation, examining only the immediate potential benefits of gene drives is insufficient. Cognizant of Stilgoe, Owen, and Macnaghten's (2013) comments on the closeted environment in which technology tends to be developed, a wider evaluation of the potential implications of using gene drives is required. Considerable scholarship exists describing the technical aspects of gene editing and gene drives, as well as discussions of regulation and potential applications (Esvelt et al. 2014; Hsu, Lander, and Zhang 2014; Oye et al. 2014; Reardon 2016). Many have examined general economic questions about transgenic pest control (e.g. National Research Council 2010) or basic efficiency implications of self-limiting versus self-sustaining transgenic control (Mumford and Carrasco 2014), but little research examining the broader socioeconomic implications of gene drives exists.

Applications of gene drives will have profound economic implications, comparable to the Green Revolution or crop biotechnology. Multiple stakeholders will look to economics to help understand the magnitude of the benefits and costs and the type of impacts from proposed gene drive applications, as well as for policy recommendations regarding their deployment. Here, as an early contribution from economics to the discussion on the responsible use of gene drives, we describe and discuss economic issues implicated in the research, development, and proposed applications of gene drives.

The scientists and would-be innovators responsible for the technical development and deployment of gene drives are among our intended audience. Responsible innovation would seem to require that the process of technology development be part of the evaluation of the potential costs and benefits. This aspect of innovation is particularly important for gene drive technology that involves manipulation of genetic material, since for many people the existence of such technologies contributes to the perception of the world as an inherently risky place.

This paper describes four political economy issues likely to be important in the responsible deployment of gene drives, for goals such as eradication or management of mosquito-vectored human diseases, elimination of invasive rodents on islands, and mitigation of the effects of agricultural insect pests.

First, the technical aspects of gene drives will greatly influence the governance and regulation of a gene drive industry, but social factors surrounding gene drives will play significant roles, particularly public perceptions, so that social science research can make key contributions. Second, gene drive applications will generate negative social impacts that will at least partially offset the benefits. Third, economic surplus, the standard yardstick of economic measurement, is a useful but incomplete measure of the net benefits of gene drive applications. Fourth, the nature of the technology and the nascent stage of its development imply dynamic nonlinearities that complicate conventional theory on economic supply and demand, making policy recommendations more difficult to develop. To illustrate this last point, we use a stylized conceptual model of the marginal costs and benefits of different scales of gene drive deployment to demonstrate the variety of possible deployment outcomes and the difficulty for making predictions and policy recommendations.

Cognitive maps (Figures S1–S3) capture the wider networks of cause and effect that may influence deployment of gene drives in the three contexts examined here: human diseases, agricultural pests, and invasive species (Axelrod 1976). Readers can refer to them as graphical summaries of many of the potential pros and cons and drivers and impediments of gene drive deployment raised in the remaining sections of the paper.

Incentives, technology and the governance, regulation, and perceptions of gene drives

The genetic, biological, and ecological aspects of the technology will only partly determine the governance and regulation of a gene drive industry – social factors will also play key roles, particularly public perceptions of the technology and of the industry. As a result, social science research is needed to develop more informed strategies for deploying gene drives and so better fulfill their benefits.

Incentives and self-sustaining versus self-limiting gene drives

For-profit companies would need to expect to earn an adequate return on investment to justify gene drive projects, but some types of gene drive applications will not provide these incentives. Some gene drives are self-sustaining while others are self-limiting (Esvelt et al. 2014). A self-sustaining gene drive can theoretically spread from an initial release to eventually alter the entire population of the species. With such a gene drive, the initial release would need to generate the entire required economic return. The gene drive market for such applications would consist of competition for a relatively small number of high-value contracts. Because the set of relevant diseases to eradicate or pests to manage is limited, the potential market may be quite small, and so little or no private investment would occur unless the individual contracts are of very high value. As a consequence, this type of problem may be targeted by public agencies or non-profits, or public–private partnerships.

In contrast, self-limiting gene drive applications would seem to be pre-requisite for a purely commercial gene drive industry to develop and mature. With self-limiting technologies, individual releases would have spatial and temporal limits, so that a gene drive market could develop to service multiple locations or to deliver multiple releases over time in the same region. Such a market could then attract investment to generate efficiency-enhancing innovations that would reduce costs and further expand gene drive applications. Examples of self-limiting gene drives or containment options have been proposed (Akbari et al. 2013; Esvelt et al. 2014; Schmidt and de Lorenzo 2016), but our understanding is that such methods still have technical issues to resolve and have yet to demonstrate their performance in ecologically relevant situations.

Besides allowing development of a commercial gene drive industry, self-limiting, containable, or reversible gene drives would likely be seen as safer by regulators and the general public. Hence, we expect a wide range of public and private individuals and entities to support the development and requirement of such safeguards before deployment of gene drives (Gabrieli, Smidler, and Catteruccia 2014; Oye et al. 2014; Akbari et al. 2015; Kuzma, Kokotovich, and Kuzhabekova 2016; Schmidt and de Lorenzo 2016). Private companies will likely strategically lobby for high regulatory or safety thresholds based on various types of self-limitation or containment, not only to ensure that a commercial gene drive market is possible, but also as a deterrent to competition. However, a tradeoff exists, since large corporations that can economically make the needed investments may generate negative public perceptions, potentially eroding public support for their deployment. Finally, the monopoly or market power large corporations can exert would also likely reduce the supply of gene drive deployments to be less than socially optimal.

Co-Determination of governance, regulation, and public perceptions of gene drives

Public perceptions will play a significant role in the successful deployment of gene drive applications. Potential applications of gene drive technologies seem to be quite valuable – eradicating mosquito-vectored human diseases such as malaria, effectively managing major agricultural pests without the use of pesticides, and helping restore ecosystems impacted by invasive species. We believe, however, that the obvious value of these goals is not enough to ensure successful use of gene drives, nor is scientific consensus of their value and safety. Rather, public perceptions of the technology will also matter. Two contemporary examples demonstrating this reality are the commercialization of agricultural biotechnology and policy responses to climate change. Despite solid scientific evidence for minimal human safety concerns after 20 years of widespread commercial by farmers (Shelton, Zhao, and Roush 2002; Nicolia et al. 2014; James 2015; NASEM 2016; USDA ERS 2016), negative public perceptions of crop biotechnology persist, even among scientists (Hilbeck et al. 2015; Wunderlich and Gatto 2015). As a result, many valuable crop and agricultural biotechnology applications remain underutilized or unavailable. Similarly, widespread disbelief in human-caused climate change exists in the US and other nations, despite the extensive data and scientific consensus, and these perceptions have played a significant role in political and social opposition to efforts and policies to mitigate climate change (Swim et al. 2009; Engels et al. 2013; Rejesus et al. 2013; van der Linden et al. 2015).

Even a cursory examination of the introduction of genetically engineered crops reveals how much public perceptions matter in relation to the widespread use of such technologies. Perceptions are formed from a far wider set of influences than scientific evidence and do not need to be accurate or evidence-based to have significant societal impacts. Furthermore, science communication research demonstrates that the issue is more than a simple 'information deficit' problem in which people simply need to be properly informed for their perceptions to change to a more accurate reflection of known facts (Bucchi 2008; Mohr and Toping 2010). Expertise in strategic communication to understand and manage the social construction of private perceptions among the public will be important for the successful application of gene drives. Research along these lines exists for other issues (e.g. Maibach, Roser-Renouf, and Leiserowitz 2008), but research specific to gene drives and their applications is needed to better understand the formation of individual perceptions if would-be developers want to understand the role that perceptions may play in deciding the fate of their innovations. Research of this sort is underway, associated with both private and public projects where gene drives and similar technologies are being considered (Subramaniam et al. 2012; Amin and Hashim 2015; Teiken et al. 2015), but more is needed.

The regulation and governance of gene drive applications will have significant impacts on public perceptions. Regulation addresses various market failures, such as misalignment of public interests and private incentives for human and environmental safety. However, regulations increase the cost of technology development and thus indirectly determine the types of organizations that can develop, commercialize or implement gene drive applications. In turn, the types of the organizations developing the technology affect perceptions of the technology.

For example, would-be registrants of biotech crop varieties must complete a lengthy evaluation process to demonstrate that environmental and human health are not threatened by their technology products. In the early 2000s, the cost to commercialize a single transgenic trait in maize in the US was estimated to include \$7–\$15 million for regulatory compliance costs (Kalaitzandonakes, Alston, and Bradford 2007), with total regulatory costs estimated in the range of \$20–\$30 million (McElroy 2003). Furthermore, the time from initial discovery to earning income from product sales can range 8–15 years (McElroy 2006). More recent estimates put the regulatory costs at more than \$33 million and the average time from discovery to first commercial sales at more than 11 years (Phillips and McDougall 2016).

These costs and timelines constrain the types of companies that can afford the investment costs and are able to recover them over the commercial life of the product. Important relative to public perceptions of the acceptability of biotechnology, the regulatory costs make development and release of transgenic crops difficult for academic and government institutions and small business. Hence it is left to large corporations to pursue commercialization, and then they must focus on applications with large returns to justify the investments (McElroy 2003, 2006; Bradford et al. 2005). As a result, public perceptions of agricultural biotechnology applications have been negatively influenced, contributing to opposition to their use (Hoban 2001).

In short, regulation, governance, and public perceptions of gene drives will be co-determined. How gene drives are regulated will impact how they are deployed, which will in turn impact on how they are perceived by the public and thus influence support for these deployments and their regulation.

These issues are further complicated, since many of the most beneficial gene drive applications exist in developing nations. Regulatory systems and governance institutions differ across nations and significant cultural differences imply that public perceptions of the same gene drive application will differ among nations. As a result, the co-determination of regulation, governance, and public perceptions will differ. Furthermore, international coordination will be needed, since political boundaries do not limit the movement of most species and funding for gene drive applications may exceed the resources of a single developing nation.

Many proposed applications have substantial public good aspects, such as disease eradication or invasive species management, and most will generate impacts that will be non-exclusive at some scale. For example, using a gene drive for pest suppression on a single farm would almost certainly yield some pest suppression and benefits for neighboring farms (Hutchison 2010). Standard economic theory implies that, without corrective public policy, insufficient private incentives lead to inefficiently low provision of public goods. The extent to which public goods issues will matter for gene drives depends on context. Insufficient market incentives for deployment may be less of a problem in agricultural pest eradication applications than in environmental conservation. For example, agricultural producers in a region could potentially fund a gene drive application privately, or with a mix of public and private funds, with deployment managed by local cooperatives or non-profit corporations, all potentially in a partnership with a government agency or for-profit enterprises. Indeed, agricultural applications may be a good place to initially implement gene drives, a less controversial application to prove the concept, to build public confidence in the technology and to better understand the factors determining public perceptions. On the other hand, beginning with lower value projects may doom gene drives to underinvestment and few applications, as initial perceptions of their low benefits become self-fulfilling. Social science research is needed to develop more informed strategies for deploying gene drives so that their benefits can be better realized.

Tradeoffs and unintended consequences of gene drives

Likely the most exciting application of gene drives is the potential to control or eradicate mosquito-vectored human diseases such as malaria, dengue, Zika, and a variety of other arthropod-vectored diseases (Esvelt et al. 2014). Given the estimate of almost 200 million cases of malaria in 2013 and the 584,000 human deaths (WHO 2014), controlling or eradicating malaria alone would generate tremendous value using any reasonable economic measure (Gallup and Sachs 2001; Sachs and Malaney 2002). With thousands of people dying and hundreds of millions ill, it seems reasonable to assume that preventing these deaths and illness would be beneficial.

This type of logic drove the Green Revolution as the way to address the existence of millions of poor, starving people in the world. Norman Borlaug, the 'Father of the Green Revolution,' received the Nobel Peace Prize in 1970 and is widely credited with saving a billion people from starvation by bringing modern agricultural varieties, inputs, and methods to developing nations, especially Asia and Latin America (Hesser 2006). The person or persons credited with using gene drives to eradicate insect-vectored diseases will possibly be remembered in a similar fashion. Other examples of such technologies include vaccinations and medical antibiotics.

The Green Revolution has been examined by several economists and so provides a useful comparison for the potential impact of disease eradication. Helping nations feed their starving populations and thus avoiding the associated human misery has obvious parallels with eradicating malaria and similar diseases to prevent thousands of deaths and millions of debilitating illnesses each year. The benefits of the Green Revolution have been documented (Evenson and Gollin 2003). As the euphoria of the initial increases in grain production began to wear off, many started to look more critically at the wider effects of the Green Revolution, finding negative social impacts, not just benefits. Issues noted included that the core problem was wider than just feeding people: infrastructure limitations to deal with the added grain and people, increased resource demands and instability, and inequity in the distribution of benefits (Wharton 1969; Falcon 1970; Wade 1974; Conway and Barbier 1988). If gene drives were used to eradicate or greatly reduce mosquito-vectored diseases, similar critical examinations of the impacts likely would occur and not all the findings would be positive, though the problems of abundance are often preferable to those of scarcity.

If the societies in affected regions are adapted to the presence of these diseases, much as many societies were adapted to perennial food scarcity or the potential for famine, removing the diseases might be disruptive, requiring these societies to adapt. Not only would existing resources need to be reallocated, but total resource needs would also increase. If reductions in mortality are not accompanied by commensurate reductions in birth rates, the local demand for food and infrastructure would necessarily increase, implying more local resources for agriculture, housing, transportation, and other needs, along with demand for more financial capital to import additional resources. Reducing the burden imposed by vector-borne diseases may even lead paradoxically to increased demands on the health care system overall as the larger population shifts existing resources away from caring for those who are ill with the eradicated diseases to other health care needs. Also, the education system would need more resources and the economy would have to grow faster to provide employment for the increased number of workers entering the economy.

Increasing and reallocating resources would create issues with equity, much as occurred with the Green Revolution (Falcon 1970; Wade 1974; Conway and Barbier 1988). The benefits and the burden of providing additional resources would vary across regions and demographic groups, and resource reallocation would be subject to political, social, and economic constraints, so that the benefits and burdens would fall unevenly. Furthermore, increased resource use raises questions of increased environmental impacts and overall sustainability. In summary, societal gains arising from eradicating diseases would be offset to some extent by negative changes on other measures, such as equity and environmental degradation from increased resource use.

These wider, unintended consequences tie a seemingly narrow set of technological questions to much broader questions about whether the demographic transitions of developing countries in the twenty-first century will parallel previous transitions of now industrialized economies in the nineteenth and twentieth centuries, in which reduced birth rates followed reduced mortality rates (Maddison 1995; Galor and Weil 2000). Current UN population projections assume that all countries will eventually undertake such a transition, but the timing of these transitions is critical for determining when the human population will stabilize. The UN's current median estimate projects that by 2100 the global human population will reach over 11 billion and will still be growing, whereas the 20th percentile estimate projects world population stabilizing at 10 billion by 2090. The main factor determining this uncertainty is the timing of demographic transitions in different regions of the world, particularly in Africa where birth rates are currently highest, and where many of the proposed gene drive applications will have their greatest impact (UN 2015).

Relatedly, using gene drives to control agricultural pests may add to the effect known as Cochrane's Treadmill, an unintended consequence arising from new agricultural technologies that increase output (Cochrane 1958; Levins and Cochrane 1996). In the short-run, these production enhancing technologies increase farm-level profit for early adopters due to higher yields or lower costs. In the long-run, however, the increased profit attracts more adopters and the aggregate effect of the technology leads to larger supplies and thus to lower prices and falling income for all farmers. Only early adopters earn positive profits and then only in the short-run. The need for farmers to rush to adopt the newest technologies to stay ahead of falling real prices is the essence of Cochrane's Treadmill as a theory to explain the impact of agricultural technology on farmers (Cochrane 1958; Levins and Cochrane 1996).

This potentially negative impact of new crop technologies on farmers is not a new phenomenon (e.g. Simmonds 1979; Sobolevsky, Moschini, and Lapan 2004; Mitchell 2014). Superficially at least, deployment of gene drives to combat chronic pest or vectored disease problems does not suggest any new unintended economic consequence. Rather, such use of gene drives would likely continue the trend for modern agriculture to become dependent incrementally on an increasing number of technologies that individually at the farm level are profitable, but in aggregate can decrease prices and reduce farm income. We note the parallel between the situation for vectored diseases and agricultural pests in which the technology directly increases individual welfare, but may have more mixed aggregate effects.

Eliminating or effectively managing insect pests will also have unclear environmental impacts due to offsetting effects of intensification and expansion (Wu 1999; Goodwin and Smith 2003). Eliminating an economic pest would likely reduce the use of pesticides, generating positive direct environmental impacts, but could also indirectly increase intensification with potentially negative environmental impacts. For example, reducing crop insect damage could enhance agricultural intensification if removing a pest-induced yield constraint makes using other inputs such as fertilizer more profitable. Pest eradication could also induce agricultural expansion into currently unprofitable areas. A relevant example is eradicating the tsetse fly in Africa – mixed crop and livestock production would intensify in some regions, but more significantly, expansion into vast new regions would become feasible (Feldmann et al. 2005).

The take-home qualitative result for those developing gene drive technologies is that individual-level benefits (where technologies are typically targeted) may be partly or wholly offset by unintended, aggregate and long-term effects that play out through complex feedback loops. We have presented some examples, but others exist as well. Responsible innovators will recognize these potential effects and include them in *ex ante* assessments for developing particular technologies.

Incompleteness of economic surplus as a measure of the value of gene drives

Economic surplus is the fundamental economic measure for quantifying the benefits of technological changes gene drives (Just, Hueth, and Schmitz 2004). Surplus for a consumer is their willingness to pay for a good minus the cost paid, while surplus for a producer is the price received for selling a good minus the actual cost to produce it. Surplus at the individual level is the monetary value consumers or producers derive from the good and aggregating over all consumers and producers in a market gives the total monetary value or social welfare generated by the good for society. Typically, consumer surplus for a market is conceptualized and empirically estimated as the area above the market price and below the consumer demand curve, and producer surplus is the area below the market price and above the producer supply curve. The social welfare derived from the market is then the sum of consumer and producer surplus, which is a monetary measure of society's benefit from the production and sale of the good. The economic impact of a technology is then modeled as a shift in the supply and/or demand curves and associated changes in consumer and producer surplus (Just, Hueth, and Schmitz 2004). The specifics of the technology and the supply and demand curves determine the shifts, the overall changes in surplus, and their distribution between consumers and producers.

As an illustration, suppose a gene drive eliminates an agricultural insect pest, which shifts the crop supply curve outward/downward, since for any given market price, farmers could supply more of the crop. The shift from supply curve S_0 to S_1 in Figure 1 illustrates this change, which implies an equilibrium price change from P_0 to P_1. If this change is the only effect of the technology and the analysis examines this market in isolation, then the effect on social welfare of the gene drive solution is the net increase in consumer and producer surplus. Initially, consumer surplus is area A and producer surplus is area B equal to B_1 plus B_2. After pest eradication, consumer surplus is area A plus B_1 plus C_1, while producer surplus is area B_2 plus C_2. In terms of Figure 1, this increase in economic surplus is area C equal to C_1 plus C_2, which are the monetary benefits of the gene drive to society. In terms of the distribution of these benefits, consumers gain area C_1 from the increased productivity due to the gene drive, plus they gain B_1 from producers due to a lower equilibrium price. On the other hand, producers gain area C_2 from the increased productivity due to the gene drive, but lose area B_1 to consumers due to a

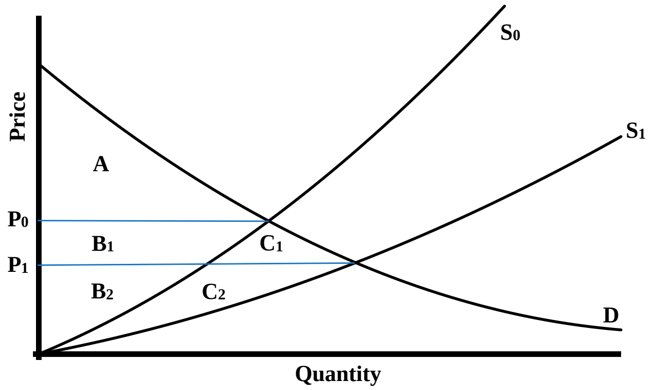

Figure 1. Change in consumer surplus and producer surplus due to supply curve shift from S_0 to S_1 for a given demand curve D, with initial equilibrium price P_0 and new equilibrium price P_1.

lower equilibrium price. The gene drive not only generates additional surplus, which is divided between consumers and producers, but it also reduces the equilibrium price, which implies a shift of existing surplus from producers to consumers (this shift illustrates the effect of Cochrane's Treadmill). The magnitude and nature of the supply curve shift due to the gene drive and the relative slopes and shape of the supply and demand curves determine the size of the benefits and their distribution among consumers and producers.

This simple example does not illustrate all the possibilities, since demand could also change (for example, in response to consumer perceptions about the technology), or both supply and demand could shift in different ways than those illustrated depending on the nature of the technology. Further elaboration lies beyond scope of this paper. This description also glosses over many theoretical and technical details and many refinements and extensions exist, such as incorporating multiple interrelated markets, non-competitive markets, externalities, international trade, and uncertainty (Just, Hueth, and Schmitz 2004). Non-market valuation methods have been developed, also based on economic surplus, to measure the benefits of technologies with externalities when markets do not exist or are incomplete (Champ, Boyle, and Brown 2003).

The next section examines some theoretical issues related to externalities in the case of gene drives. Our aim is to raise awareness of these issues so that would-be innovators are at least primed with some relevant economic questions. Given its central importance in economic analysis and the fact that any evaluation of technology within a framework of responsible innovation ought to include an economic component, we highlight some of the limitations of economic surplus as a measure of the benefits of gene drives.

Economic surplus is a monetary measure based on material well-being as derived from the production and consumption of goods and services. The data needed to calculate such measures are readily available in most economies and the results expressed as monetary values are easy to interpret. However, other factors besides income and the implied material consumption affect individual well-being and social welfare. In particular, beyond partition into components for consumers and producers, the distribution of economic surplus among potential beneficiaries is not reflected in typical surplus calculations. As previously noted, real or perceived inequalities in the distribution of surplus are likely to be important for potential uses of gene drives. Previous technological revolutions in agriculture have been accompanied by dramatic consolidation (Just 2000), and a lack of equity in the distribution of the benefits has been among the primary criticisms of the Green Revolution (Falcon 1970; Wade 1974; Conway and Barbier 1988) and genetic modification (Giannakas and Fulton 2002).

Responsible innovators evaluating gene drives may want to base their evaluation on broader economic measures than surplus, such as the Human Development Index (HDI). The HDI integrates life expectancy and educational achievement with gross domestic product (GDP) to measure the well-being of a society (UNDP 1990; Anand and Sen 1994). Since its initial release in 1990, the HDI has generated a variety of proposed refinements and alternatives, as well as criticisms and critiques (Hicks 1997; Noorbakhsh 1998; Sagar and Najam 1998; Ranis, Stewart, and Samman 2006; Stanton 2007). The HDI or similar measures have typically been applied at national levels, either as substitutes for or improvements in using GDP (Crafts 2002; Despotis 2005; Bray et al. 2012), and to evaluate general policies or strategies (Davies and Quinlivan 2006; Self and Grabowski 2007; Davies 2009). We know of no applications of the HDI or similar indices to evaluate the impact of a specific new technology, likely because of the difficulty in estimating how the technology would impact measures such as life expectancy and educational attainment.

Another approach for improving measures of social well-being has been to develop measures of happiness and to examine their relation to income and the HDI (e.g. Easterlin 1995, 2003; Blanchflower and Oswald 2005; Kahneman et al. 2006; Leigh and Wolfers 2006; Easterlin et al. 2010). The emerging consensus is that once income reaches some level of sufficiency, further increasing income has little or no positive impact on subjective measures of happiness (Kahneman et al. 2006; Easterlin et al. 2010). The primary mechanisms for this Easterlin Paradox are adaptation to new income levels and increasing aspirations driven by relative income compared with a rising reference group, which together create a Hedonic Treadmill (Knight 2012). Here, it appears that consideration of the responsible adoption of gene drive technology has identified a methodological gap in the relevant economic toolkit. The potential reductions in mortality and morbidity resulting from disease eradication, reduction in impacts on agriculture, and abatement of invasive species would seem to be excellent cases for empirical studies to document how measures of subjective well-being improve over time, even in nations with relatively high per capita income. Thus, the advent of gene drives would appear to provide an important incentive for the development of economic tools generally useful in the analysis of responsible innovations.

A model of knowledge spillovers and initial conditions in gene drive deployment

Beyond the issues raised above, gene drive deployments have the potential for nonlinear economic dynamics that complicate the analysis of how gene drives might affect social welfare. To illustrate this point, we present a stylized conceptual model of a market for gene drive services, based on the costs and benefits of different scales of gene drive deployment across a range of applications. The Supplement provides further technical detail.

Model description

The stylized gene drive market consists of societal demand for gene drives by public entities such as government agencies and NGOs (e.g. conservation organizations, farmer cooperatives), and firms to supply these gene drives. Societal demand for gene drives depends inversely on the price to 'buy' a gene drive. When this price is high, only a few gene drive applications are demanded and only the most beneficial. However, as the price for gene drives decreases, the total number of gene drives demanded increases to include those providing lower benefits, with the additional societal benefits from adding another gene drive declining with each additional deployment. This logic implies a standard downward sloping demand curve with lower total demand with high prices and vice versa.

Firms supply gene drives as long as the price they receive for 'selling' the gene drive deployment exceeds their costs. Multiple firms exist that could provide a gene drive and the 'buyer' will be cost conscious and choose the lowest cost provider. In a conventional model, most applicable to well-established industries, the supply curve slopes upward (or at least remains flat), since each additional gene drive application comes at a greater cost than the last.

In a standard model, these economic forces of supply and demand are in equilibrium at the intersection of the supply and demand curves, with this intersection defining an economically efficient level of gene drive deployment and the price to deliver it. Figure 2 illustrates this conventional model, with the scale of gene drive deployment on the horizontal axis as the quantity and the additional societal benefit or industry cost for an additional gene drive on the vertical axis as the price expressed as dollars per deployment. With this stylized market, economic surplus is the standard measure of the net benefits of gene drives for society.

This traditional model of the cost structure underlying the industry supply curve has substantial empirical and theoretical support for industries built on mature technologies.

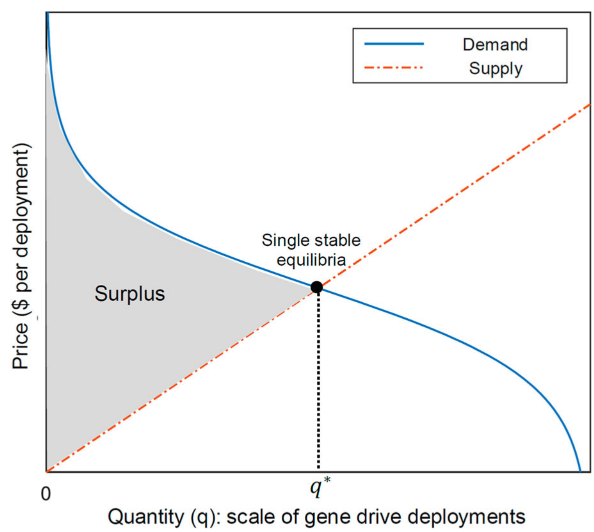

Figure 2. Equilibrium and economic surplus for a stylized gene drive market with a conventional model of deployment costs.

However, for industries built on nascent technologies such as gene drives, the relationship between costs and number of deployments may not behave in this manner. Rather, economies of scale likely exist that imply a downward sloping supply curve – the cost of each new gene drive deployment is less than the last. The underlying logic for this relationship is that early in the commercialization process, with each new application, innovators learn from their own experience ('learning-by-doing') and from observing others, which makes subsequent applications easier and less costly. These learning-by-doing and social network effects among innovators lead to knowledge spillovers across firms so that the industry supply curve is downward sloping in price – each additional application decreases the cost of the next application for all firms (Durlauf 1991; Jaffe, Trajtenberg, and Henderson 1993). This situation will likely apply to gene drives, at least initially. These additional costs are not purely technical, but also the costs for public engagement in deployment areas, managing public relations and the costs of satisfying regulatory requirements and working with local regulatory agencies. As experience with the technology grows, these costs would decline as well.

Figure 3 illustrates an example, with a more technical description in the Supplement. A downward sloping supply curve due to knowledge spillovers (or other factors) implies that multiple equilibria for the scale of gene drive deployment become possible, with initial conditions determining which equilibrium is realized. In Figure 3, three equilibria exist (q_1, q_2, and q_3). The equilibrium at q_1 is a stable, low-deployment equilibrium. Any initial gene drive deployment scale less than q_1 could attract funding or find a buyer, since the additional benefits (demand) would exceed the costs to the company to deploy it (supply), and so the gene drive market would grow until $q = q_1$. However, the extra cost to deploy the next gene drive beyond q_1 would exceed the additional benefits to society of this gene drive, and so funding would not be available. As a result, with any initial gene drive deployment between q_1 and q_2, the market would shrink until

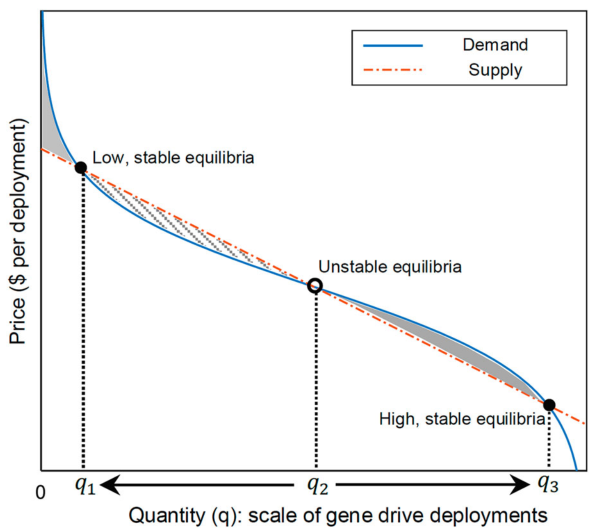

Figure 3. Equilibria and economic surplus for a stylized gene drive market with knowledge spillovers for deployment costs.

$q = q_1$. The surplus obtained at the q_1 equilibrium is the first solid gray area on the left. If for some reason deployment was at q_2, for example due to government-sponsored R&D and gene drive deployments, the additional benefits to society for the next gene drive beyond q_2 would exceed the extra cost to deploy this gene drive. As a result, with any initial gene drive deployment between q_2 and q_3, the market would grow until $q = q_3$, while the market would shrink until $q = q_3$ with any initial deployment beyond q_3. The equilibrium at q_3 is a stable, high-deployment equilibrium, while the equilibrium at q_2 is unstable. The surplus obtained at the q_3 equilibrium is the sum of the two solid gray areas, less the hatched gray area. These results demonstrate that this particular arrangement creates two stable equilibria – a low-deployment and a high-deployment level. The importance of initial conditions in determining which equilibrium obtains is often referred to as 'path dependency' (Barro and Sala-i-Martin 1995; Martin and Sunley 2006).

Note that the value of the model here is not so much that it accurately reflects exactly how the economics of gene drive technology will play out, but that it embodies some important points for would-be innovators and regulators to consider. Most importantly, the possibility of a downward sloping supply curve due to knowledge spillovers can lock the possibility of low gene drive deployment into the economic landscape as a high-level unintended consequence. The type of knowledge spillover in question – that the heavy regulatory lifting and path clearing among the public done by initial innovators provides lessons from which later innovators can learn, making subsequent innovations easier and less costly – is a common belief among those involved in technology innovation. The model shows that even while this belief may be well-founded, under rather mild assumptions about the relationship between supply (marginal expected costs) and demand (marginal expected benefits), the potential exists for the existence of economic attractors in the adoption dynamics that lock technology into low-benefit, low-deployment traps.

This simple model also provides a way to understand some of the wider economic issues to consider in a responsible evaluation of gene drives. Many of the previous points made in this paper could be couched in terms of this model. For example, one way to understand how public perceptions may play a role is via initial conditions. If the way the technology is introduced to the public leads to a high degree of skepticism, then the low-level deployment equilibrium is likely to occur. However, more inclusive approaches to technology development with high levels of public engagement may potentially create high levels of initial deployment that eventually lead to the high-deployment equilibrium. Furthermore, which of the two stable equilibria is desirable from an economic perspective depends on the relative sizes of the gains and losses in economic surplus as indicated by the solid and hatched gray areas in Figure 3.

Modeling a divergence between public and private incentives

As illustrated in Figure 3, the model assumes that marginal private benefits and costs facing firms align with the marginal social benefits and costs, i.e. firms' incentives align with public payoffs. However, gene drive deployments will almost certainly provide public goods and create various positive and negative externalities, implying divergences between private incentives and social payoffs. As a result, the demand curve defined by the additional societal benefits obtained from another gene drive deployment will not match the additional private benefits a firm will earn from the same deployment, nor will the supply curve defined by the added costs to the firm for providing another gene drive deployment match the social costs.

The social costs for an additional gene drive deployment may exceed the private costs due to negative externalities, such as ecological impacts beyond the target species, fears among some groups due to the release of a gene drive in their region, or that gene drives will speed up of Cochrane's Treadmill. When such externalities are not included in the profit maximization of individual firms or industries, the social costs from an additional gene dive deployment could easily exceed the additional private costs. However, positive externalities may also occur, such as from overly costly regulation of the technology, poorly defined intellectual property rights and 'patent thickets' that restrict firm entry (Ledford 2016). Such externalities cause private costs for an additional gene drive deployment to exceed the additional social costs, which in terms of the graphical model imply a separate public or socially preferred supply curve and a private supply curve that firms will have incentives to provide.

Divergences between the public and private benefits from each additional gene drive deployment can also occur due to public goods and externalities. The social benefits from an additional gene drive deployment may be higher than the additional private benefits due to an array of public goods aspects of gene drive deployment. For example, applications that carry a high social benefit, but do not offer significant market opportunities to individual firms, such as controlling invasive species in sensitive ecosystems (Genetic Engineering and Society 2015) or self-sustaining gene drives to eradicate mosquito-vectored diseases. Even with self-limiting gene drives, the additional social benefits of a gene drive may be higher than the private benefits if, for example, intellectual property protections for specific commercialized products are too weak, such that firms can free-ride on the applied research and development investments of other firms. This situation would occur if specific gene-edited insects could not be patented and if the blueprints for creating such insects were relatively easy to follow. Conversely, the additional social benefits could be lower than the private benefits when overly strong intellectual property rights create inefficient levels of market power and monopoly power for some firms. In terms of the graphical model, these types of public goods and externalities imply a separate public (socially preferred) demand curve and a private (actually realized) demand curve.

Figure 4 illustrates one example of the possibilities when this stylized model incorporates externalities. For tractability, assume a large divergence between the private demand curve (the marginal private benefits of gene drives) and the public demand curve (the marginal social benefits of gene drives) due to externalities (and/or public goods). In Figure 4, private benefits define the private demand curve D_p, while societal benefits define a demand curve that is either lower (D_L) or higher (D_H) than the private demand curve. This divergence creates nonlinearities in the existence, uniqueness, and stability of the predicted equilibria relative to the social optima.

The relevance of the nonlinearities can be seen by examining the effect of using traditional economic policy instruments to align the private demand curve D_p with the societal demand curve (D_L or D_H). Standard economic theory suggests that Pigovian taxes or subsidies correct externalities by aligning private costs or benefits with their

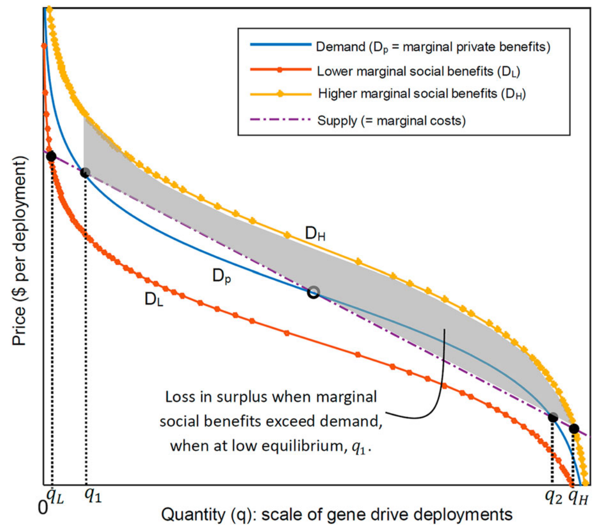

Figure 4. Equilibria and economic surplus for a stylized gene drive market with externalities causing a large divergence between social and private benefits.

social counterparts. In Figure 4, if the social benefits for each additional gene drive are sufficiently lower than the private benefits, then only a low-deployment equilibrium (q_L) characterizing the social optimum exists. Conversely, if social benefits for each additional gene drive are sufficiently higher than the private benefits, then only the high-level deployment equilibrium (q_H) exists and is efficient based on economic surplus. However, suppose that social benefits of gene drives (D_H) are higher than private benefits (D_p) and deployment is stuck at the low equilibrium (q_1) prior to a policy change (e.g. due to initial skepticism from the public). If a technology subsidy (e.g. for research and development) is implemented to align private benefits (D_p) with the higher social benefits (D_H), then expected gene drive deployment would move to the single high equilibrium (q_3), leading to a nonlinear jump in surplus (solid shaded area in Figure 4).

The Supplement provides another case in which the multiple equilibria, combined with an externality, make traditional economic policy instruments that realign private incentives with their social counterparts insufficient for achieving the socially optimal outcome. As a result, additional policy instruments may be needed to 'flip' the system trapped in a sub-optimal equilibrium, even after private incentives have been realigned.

This stylized model shows that multiple equilibria may exist for gene drive deployments and that nonlinearities may arise, possibilities that policy actions should take into account. Gene drive deployments may 'flip' between states rapidly or fall back to a low equilibrium, even after large sums of private and public spending in an attempt to reach socially preferable, high-deployment states. Overall, these results suggest that relevant economic and social uncertainties exist regarding the behavior of a nascent gene drive industry and the regulation needed to achieve desirable social outcomes, comparable to the technical and ecological uncertainties regarding the behavior of gene drives in actual organisms, populations, and ecosystems. As a result, flexible and responsive regulation would seem to be appropriate as empirical research helps resolve some of the social, economic and other uncertainties surrounding gene drives.

Conclusion

Gene drives made possible by accurate gene editing technologies offer considerable promise for making substantial improvements in the human condition globally, including eradicating mosquito-vectored human diseases, invasive species on islands, and serious agricultural insect pests. Several papers (including some in this special issue) describe the technical aspects of gene editing and gene drives and discuss their regulation and potential applications, but little work exists about economic issues surrounding gene drives. New technologies should be deployed in a responsible manner, and economics as an academic discipline can make contributions in this regard. Here we described and discussed four economic issues that would-be innovators and regulators should consider as part of a broad economic evaluation of gene drives within a framework of responsible innovation. Many of the arguments surrounding the wider set of issues connected with the use of gene drives were captured in prototype cognitive models to help further discussion and debate, plus a stylized economic model was used to more formally integrate these issues into traditional economic rubrics.

First, whether a gene drive is self-limiting or self-sustaining will greatly influence the governance and regulation of a gene drive industry, but social factors surrounding gene drives will play significant roles, particularly public perceptions. Self-limiting gene drives would seem to be a requirement for a private commercial gene drive industry to develop, and would likely better satisfy safety and ethical concerns of many stakeholders. However, empirical and theoretical social science research is needed to understand public perceptions and how they differ culturally, and how regulation, governance, and public perceptions co-determine one another.

Second, gene drive applications will generate unintended negative social impacts that will at least partially offset the benefits. Discussion focused on equity in the distribution of the benefits generated by gene drives and the likelihood of more intensive and expansive resource use. As gene drives come closer to deployment, policymakers and other stakeholders will likely want research quantifying the tradeoffs and unintended consequences of specific applications.

Third, economic surplus is a convenient and useful summary measure of benefits that economists traditionally use to capture material well-being, but it misses other aspects of the quality of life that may be more relevant to the economic assessment of gene drives. Broader measures exist, such as the HDI or subjective measures of happiness, for which the proposed applications of gene drives are good candidates for innovative empirical policy analysis. Solutions filling this gap in available methodologies will have value in the field of responsible innovation and potentially stimulate solving a much wider class of problems.

Fourth, the nature of gene drives and the nascent stage of their development imply nonlinearities that make identifying economic equilibria and general policy recommendations challenging. A stylized economic model of gene drive development illustrated the wide variety of possible outcomes and the resulting difficulty in making predictions and recommendations. The immediate and potentially substantial benefits of gene drives and the genetic, ecological, social, and economic uncertainties suggest that a responsible course of action is to move forward, maintaining both regulatory flexibility and conducting empirical and applied research to resolve some of these uncertainties.

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References

Akbari, O. S., Bellen, H. J., Bier, E., Bullock, S. L., Burt, A., Church, G. M., Cook, K. R., et al. 2015. "Safeguarding Gene Drive Experiments in the Laboratory." *Science* 349: 927–929.

Akbari, O. S., K. Matzen, J. Marshall, H. Huang, C. Ward, and B. Hay. 2013. "A Synthetic Gene Drive System for Local, Reversible Modification and Suppression of Insect Populations." *Current Biology* 23: 671–677.

Amin, L., and H. Hashim. 2015. "Factors Influencing Stakeholders Attitudes Toward Genetically Modified Aedes Mosquito." *Science and Engineering Ethics* 21: 655–681. doi:10.1007/s11948-014-9557-5.
Anand, S., and A. K. Sen. 1994. *Human Development Index: Methodology and Measurement*. No. HDOCPA-1994-02. New York: Human Development Report Office (HDRO), United Nations Development Programme (UNDP).
Axelrod, R. 1976. "The Cognitive Mapping Approach to Decision Making." In *Structure of Decision: The Cognitive Maps of Political Elites*, edited by R. Axelrod, 3–17. Princeton, NJ: Princeton University Press.
Barro, R. J., and X. Sala-i-Martin. 1995. *Economic Growth*. Cambridge, MA: MIT Press.
Blanchflower, D. G., and A. J. Oswald. 2005. "Happiness and the Human Development Index: The Paradox of Australia." *Australian Economic Review* 38: 307–318.
Bradford, K. J., A. Van Deynze, N. Gutterson, W. Parrot, and S. H. Strauss. 2005. "Regulating Transgenic Crops Sensibly: Lessons from Plant Breeding, Biotechnology and Genomics." *Nature Biotechnology* 23: 439–444.
Bray, F., A. Jemal, N. Grey, J. Ferlay, and D. Forman. 2012. "Global Cancer Transitions According to the Human Development Index (2008-2030): A Population-based Study." *The Lancet: Oncology* 13: 790–801. doi:10.1016/S1470-2045(12)70211-5.
Bucchi, M. 2008. "Of Deficits, Deviations, and Dialogues." In *Handbook of Public Communication of Science and Technology*, edited by M. Bucchi and B. Trench, 57–76. New York, NY: Routledge.
Champ, P. A., K. J. Boyle, and T. C. Brown. 2003. *A Primer on Nonmarket Valuation*. Dordrecht: Kluwer Academic.
Cochrane, W. W. 1958. *Farm Prices: Myth and Reality*. St. Paul: University of Minnesota Press.
Conway, G. R., and E. B. Barbier. 1988. "After the Green Revolution: Sustainable and Equitable Agricultural Development." *Futures* 20: 651–670.
Crafts, N. 2002. "The Human Development Index, 1870-1999: Some Revised Estimates." *European Review of Economic History* 6: 395–405.
Davies, A. 2009. "Human Development and the Optimal Size of Government." *Journal of Socio-Economics* 38: 326–330.
Davies, A., and G. Quinlivan. 2006. "A Panel Data Analysis of the Impact of Trade on Human Development." *Journal of Socio-Economics* 35: 868–876.
Despotis, D. K. 2005. "A Reassessment of the Human Development Index via Data Envelopment Analysis." *Journal of the Operational Research Society* 56: 969–980.
Durlauf, S. N. 1991. "Multiple Equilibria and Persistence in Aggregate Fluctuations." *American Economic Review* 81 (2): 70–74.
Easterlin, R. A. 1995. "Will Raising the Incomes of All Increase the Happiness of All?" *Journal of Economic Behavior and Organization* 27: 35–47.
Easterlin, R. A. 2003. "Explaining Happiness." *Proceedings of the National Academy of Sciences* 100: 11176–11183. doi:10.1073\pnas.1633144100.
Easterlin, R. A., L. A. McVey, M. Switek, O. Sawangfa, and J. S. Zweig. 2010. "The Happiness-Income Paradox Revisited." *Proceedings of the National Academy of Sciences* 107: 22463–22468. doi:10.1073/pnas.1015962107.
Engels, A., O. Huther, M. Schafer, and H. Held. 2013. "Public Climate-Change Skepticism, Energy Preferences and Political Participation." *Global Environmental Change* 23: 1018–1027. doi:10.1016/j.gloenvcha.2013.05.008.
Esvelt, K. M., A. L. Smidler, F. Catteruccia, and G. M. Church. 2014. "Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations." *eLife* 3: 20131071. doi:10.7554/eLife.03401.
Evenson, R. E., and D. Gollin. 2003. "Assessing the Impact of the Green Revolution, 1960 to 2000." *Science* 300: 758–762. doi:10.1126/science.1078710.
Falcon, W. P. 1970. "The Green Revolution: Generations of Problems." *American Journal of Agricultural Economics* 52 (5): 698–710.
Feldmann, U., V. A. Dyck, R. C. Mattioli, and J. Jannin. 2005. "Potential Impact of Tsetse Fly Control Involving the Sterile Insect Technique." In *Sterile Insect Technique Principles and*

Practice in Area-Wide Integrated Pest Management, edited by V. A. Dyck, J. Hendrichs, and A. S. Robinson, 701–723. Dordrecht: Springer.

Florax, R. J. G. M., C. M. Travisi, and P. Nijkamp. 2005. "A Meta-Analysis of the Willingness to Pay for Reductions in Pesticide Risk Exposure." *European Review of Agricultural Economics* 32 (4): 441–467.

Gabrieli, P., A. Smidler, and F. Catteruccia. 2014. "Engineering the Control of Mosquito-Borne Infectious Diseases." *Genome Biology* 15: 535. https://www.biomedcentral.com/track/pdf/10.1186/s13059-014-0535-7?site=genomebiology.biomedcentral.com.

Gallup, J. L., and J. D. Sachs. 2001. "The Economic Burden of Malaria." *American Journal of Tropical Medicine and Hygiene* 64: 85–96.

Galor, O., and D. N. Weil. 2000. "Population, Technology, and Growth: From Malthusian Stagnation to the Demographic Transition and Beyond." *American Economic Review* 90 (4): 806–828.

Genetic Engineering and Society. 2015. *Conserving Island Biodiversity*. Raleigh: Genetic Engineering and Society, North Carolina State University. Accessed April 30, 2016. https://research.ncsu.edu/islandmice/.

Giannakas, K., and M. Fulton. 2002. "Consumption Effects of Genetic Modification: What if Consumers are Right?" *Agricultural Economics* 27: 97–109. http://www.sciencedirect.com/science/article/pii/S0169515002000336.

Goodwin, B. K., and V. H. Smith. 2003. "An Ex-Post Evaluation of the Conservation Reserve, Federal Crop Insurance, and Other Government Programs: Program Participation and Soil Erosion." *Journal of Agricultural and Resource Economics* 28: 201–216.

Hales, S., N. de Wet, J. Maindonald, and A. Woodward. 2002. "Potential Effect of Population and Climate Changes on Global Distribution of Dengue Fever: An Empirical Model." *The Lancet* 360: 830–834.

Hesser, L. 2006. *The Man Who Fed the World*. Dallas, TX: Durban House.

Hicks, D. A. 1997. "The Inequality-Adjusted Human Development Index: A Constructive Proposal." *World Development* 25: 1283–1298.

Hilbeck, A., R. Binimelis, N. Defarge, R. Steinbrecher, A. Székács, F. Wickson, M. Antoniou, et al. 2015. "No Scientific Consensus on GMO Safety." *Environmental Sciences Europe* 27 (4): 1–6. doi:10.1186/s12302-014-0034-1.

Hoban, T. J. 2001. "American Consumers' Awareness and Acceptance of Biotechnology." In *National Agricultural Biotechnology Council Report 13: Genetically Modified Food and the Consumer*, edited by A. Eaglesham, S. G. Pueppke, and R. W. F. Hardy, 108–120. Ithaca, NY: NABC. Accessed April 30, 2016. http://farmfoundation.info/news/articlefiles/1069-02-08.pdf#page=108.

Hsu, P. D., E. S. Lander, and F. Zhang. 2014. "Development and Applications of CRISPR-Cas9 for Genome Engineering." *Cell* 157: 1262–1278. doi:10.1016/j.cell.2014.05.010.

Hutchison, W. D., Burkness, E. C., Mitchell, P. D., Moon, R. D., Leslie, T. W., Fleischer, S. J., Abrahamson, M., et al. 2010. "Areawide Suppression of European Corn Borer with Bt Maize Reaps Savings to Non-Bt Maize Growers." *Science* 330 (6001): 222–225.

Jaffe, A. B., M. Trajtenberg, and R. Henderson. 1993. "Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations." *Quarterly Journal of Economics* 108: 577–598.

James, C. 2015. *Global Status of the Commercialization of Biotech/GM Crops: 2015: Executive Summary*. ISAAA Brief No. 51-2015. Ithaca, NY: ISAAA. Accessed April 4, 2016. http://www.isaaa.org/resources/publications/briefs/51/executivesummary/.

Just, R. 2000. "Industrialization and Consolidation in the U.S. Food Sector: Implications for Competition and Welfare." *American Journal of Agricultural Economics* 82 (5): 1087–1104.

Just, R., D. L. Hueth, and A. Schmitz. 2004. *The Welfare Economics of Public Policy*. Northampton, MA: Edward Elgar.

Kahneman, D., A. B. Krueger, D. Schkade, N. Schwarz, and A. A. Stone. 2006. "Would You Be Happier If You Were Richer? A Focusing Illusion." *Science* 312: 1908–1910. doi:10.1126/science.1129688.

Kalaitzandonakes, N., J. M. Alston, and K. J. Bradford. 2007. "Compliance Costs for Regulatory Approval of New Biotech Crops." *Nature Biotechnology* 25: 509–511. doi:10.1038/nbt0507-509.

Knight, J. 2012. "Economic Growth and the Human Lot." *Proceedings of the National Academy of Sciences* 109: 9670–9671. doi:10.1073/pnas.1207683109.
Kuzma, J., A. Kokotovich, and A. Kuzhabekova. 2016. "Attitudes Towards Governance of Gene Editing." *Asian Biotechnology and Development Review* 18: 69–92.
Ledford, H. 2016. "Bitter Fight Over CRISPR Patent Heats Up." *Nature* 529: 265–265. doi:10.1038/nature.2015.17961.
Leigh, A., and J. Wolfers. 2006. "Happiness and the Human Development Index: Australia Is Not a Paradox." *Australian Economic Review* 39 (2): 176–184.
Levins, R. A., and W. W. Cochrane. 1996. "The Treadmill Revisited." *Land Economics* 72: 550–553.
Lobell, D. B., M. J. Roberts, W. Schlenker, N. Braun, B. B. Little, R. M. Rejesus, and G. L. Hammers. 2014. "Greater Sensitivity to Drought Accompanies Maize Yield Increase in the U.S. Midwest." *Science* 344: 516–519. doi:10.1126/science.1251423.
Lobell, D. B., W. Schlenker, and J. Costa-Roberts. 2011. "Climate Trends and Global Crop Production since 1980." *Science* 333: 616–620. doi:10.1126/science.1204531.
Lovell, S. J., and S. F. Stone. 2005. *The Economic Impacts of Aquatic Invasive Species: A Review of the Literature*. Working Paper # 05-02. Washington, DC: National Center for Environmental Economics, U.S. Environmental Protection Agency.
Maddison, A. 1995. *Monitoring the World Economy, 1820-1992*. Paris: OECD.
Maibach, E. W., C. Roser-Renouf, and A. Leiserowitz. 2008. "Communication and Marketing as Climate Change-Intervention Assets: A Public Health Perspective." *American Journal of Preventative Medicine* 35: 488–500. doi:10.1016/j.amepre.2008.08.016.
Martin, R., and P. Sunley. 2006. "Path Dependence and Regional Economic Evolution." *Journal of Economic Geography* 6 (4): 395–437.
McElroy, D. 2003. "Sustaining Agbiotechnology Through Lean Times." *Nature Biotechnology* 21: 996–1002.
McElroy, D. 2006. "Valuing the Product Development Cycle in Agricultural Biotechnology – What's in a Name?" *Nature Biotechnology* 22: 817–822.
Mitchell, P. D. 2014. "Market-Level Assessment of the Economic Benefits of Atrazine in the United States." *Pest Management Science* 70: 1684–1696. doi:10.1002/ps.3703.
Mohr, P., and D. Toping. 2010. "Factoids, Factettes and Fallacies: The Problem of Crossover Research in the Analysis of Consumer Responses to Biotechnology." *New Biotechnology* 27 (6): 729–733.
Mourtzinis, S., J. E. Specht, L. E. Lindsey, W. J. Wiebold, J. Ross, E. D. Nafziger, H. J. Kandel, et al. 2015. "Climate-Induced Reduction in US-Wide Soybean Yields Underpinned by Region- and in-Season-Specific Responses." *Nature Plants* Article number 14026. doi:10.1038/nplants.2014.26.
Mumford, J. D., and L. R. Carrasco. 2014. "Economics of Transgenic Insects for Field Release." In *Transgenic Insects: Techniques and Applications*, edited by M. Q. Benedict, 306–318. Oxfordshire: CABI.
National Academies of Sciences, Engineering, and Medicine. 2016. *Genetically Engineered Crops: Experiences and Prospects*. Washington, DC: National Academies Press.
National Research Council. 2010. *The Impact of Genetically Engineered Crops on Farm Sustainability in the United States*. Washington, DC: National Academies Press.
Nicolia, A., A. Manzo, F. Veronesi, and D. Rosellini. 2014. "An Overview of the Last 10 Years of Genetically Engineered Crop Safety Research." *Critical Reviews in Biotechnology* 34 (1): 77–88.
Noorbakhsh, F. 1998. "A Modified Human Development Index." *World Development* 26: 517–528.
Olson, L. 2006. "The Economics of Terrestrial Invasive Species: A Review of the Literature." *Agricultural and Resource Economics Review* 35: 178–194.
Oye, K. A., K. Esvelt, E. Appleton, F. Catteruccia, G. Church, T. Kuiken, S. Lightfoot, J. McNamara, A. Smidler, and J. Collins. 2014. "Regulating Gene Drives." *Science* 345: 626–628. doi:10.1126/science.1254287.
Pardey, P. G., J. M. Beddow, T. M. Hurley, T. K. M. Beatty, and V. R. Eidman. 2014. "A Bounds Analysis of World Food Futures: Global Agriculture Through to 2050." *Australian Journal of Agricultural and Resource Economics* 58: 571–589.

Patz, J. A., D. Cambell-Lendrum, T. Halloway, and J. A. Foley. 2005. "Impact of Regional Climate Change on Human Health." *Nature* 438: 310–317. doi:10.1038/nature04188.

Phillips, M., and J. McDougall. 2016. *The Cost of New Agrochemical Product Discovery, Development and Registration in 1995, 2000, 2005-8 and 2010 to 2014*. Washington, DC: CropLife America. Accessed July 13, 2017. http://191hmt1pr08amfq62276etw2.wpengine.netdna-cdn.com/wp-content/uploads/2016/04/Phillips-McDougall-Final-Report_4.6.16.pdf.

Pimentel, D., R. Zuniga, and D. Morrison. 2005. "Update on the Environmental and Economic Costs Associated with Alien-Invasive Species in the United States." *Ecological Economics* 52: 273–288.

Ranis, G., F. Stewart, and E. Samman. 2006. "Human Development: Beyond the Human Development Index." *Journal of Human Development* 7: 323–358.

Reardon, S. 2016. "Welcome to the CRISPR zoo." *Nature* 531: 160–163. doi:10.1038/531155a.

Rejesus, R. M., M. Mutuc-Hensley, P. D. Mitchell, K. H. Coble, and T. O. Knight. 2013. "U.S. Agricultural Producer Perceptions of Climate Change." *Journal of Agricultural and Applied Economics* 45: 701–718.

Sachs, J., and P. Malaney. 2002. "The Economic and Social Burden of Malaria." *Nature* 415: 680–685.

Sagar, A. D., and A. Najam. 1998. "The Human Development Index: A Critical Review." *Ecological Economics* 25: 249–264.

Schmidt, M., and V. de Lorenzo. 2016. "Synthetic Bugs on the Loose: Containment Options for Deeply Engineered (Micro)Organisms." *Current Opinion in Biotechnology* 38: 90–96. doi:10.1016/j.copbio.2016.01.006.

Self, S., and R. Grabowski. 2007. "Economic Development and the Role of Agricultural Technology." *Agricultural Economics* 36: 395–404.

Shelton, A. M., J. Z. Zhao, and R. T. Roush. 2002. "Economic, Ecological, Food Safety and Social Consequences of the Deployment of Bt Transgenic Plants." *Annual Review of Entomology* 47: 845–881.

Simmonds, N. W. 1979. *Principles of Crop Improvement*. London: Longman.

Sobolevsky, A., G. Moschini, and H. Lapan. 2004. "Genetically Modified Crops and Product Differentiation: Trade and Welfare Effects in the Soybean Complex." *American Journal of Agricultural Economics* 87: 621–644.

Stanton, E. A. 2007. *The Human Development Index: A History*. Working Paper 127. Amherst: Political Economy Research Institute, University of Massachusetts-Amherst. Accessed April 30, 2016. http://www.peri.umass.edu/fileadmin/pdf/working_papers/working_papers_101-150/WP127.pdf.

Stilgoe, J., R. Owen, and P. Macnaghten. 2013. "Developing a Framework for Responsible Innovation." *Research Policy* 42: 1568–1580.

Subramaniam, T. S. S., H. L. Lee, N. W. Ahmad, and S. Murad. 2012. "Genetically Modified Mosquito: The Malaysian Public Engagement Experience." *Biotechnology Journal* 7: 1321–1323. doi:10.1002/biot.201200282.

Swim, J., S. Clayton, T. Doherty, R. Gifford, G. Howard, J. Reser, P. Stern, and E. Weber. 2009. *Psychology and Global Climate Change: Addressing a Multi-Faceted Phenomenon and Set of Challenges*. Washington, DC: American Psychological Association.

Teiken, C., P. Lemaux, B. Grafton-Cardwell, and N. McRoberts. 2015. "Genetic Engineering to Protect Citrus from HLB." *Citrograph* 6 (1): 24–31. Accessed April 30, 2016. http://citrusresearch.org/wp-content/uploads/CRB-Citrograph-Mag-Q1-2015.pdf.

Tillman, D., C. Balzer, J. Hill, and B. L. Befort. 2011. "Global Food Demand and the Sustainable Intensification of Agriculture." *Proceedings of the National Academy of Sciences* 108: 20260–20264. doi:10.1073/pnas.1116437108.

United Nation Development Programme (UNDP). 1990. *Human Development Report 1990*. New York: UNDP. Accessed April 30, 2016. http://hdr.undp.org/en/reports/global/hdr1990.

United Nations. 2015. *World Population Prospects*. New York: UN Department of Economic and Social Affairs (DESA), Population Division. Accessed April 30, 2016. http://esa.un.org/unpd/wpp/Publications/Files/Key_Findings_WPP_2015.pdf.

U.S. Department of Agriculture, Economic Research Service. 2016. *Adoption of Genetically Engineered Crops in the U.S.* Washington, DC: USDA-ERS. Accessed April 30, 2016. http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us.aspx.

van der Linden, S., A. Leiserowitz, G. D. Feinberg, and E. W. Maibach. 2015. "The Scientific Consensus on Climate Change as a Gateway Belief: Experimental Evidence." *PLoS ONE* 10 (2): e0118489. doi:10.1371/journal.pone.0118489.

Wade, N. 1974. "Green Revolution (I): A Just Technology, Often Unjust in Use." *Science* 186: 1093–1096.

Wharton, C. R. 1969. "The Green Revolution: Cornucopia or Pandora's Box?" *Foreign Affairs* 47: 464–476.

World Health Organization (WHO). 2014. "World Malaria Report 2014". WHO. Accessed April 30, 2016. http://www.who.int/malaria/publications/world_malaria_report_2014/report/en/.

Wu, J. 1999. "Crop Insurance, Acreage Decisions, and Nonpoint-Source Pollution." *American Journal of Agricultural Economics* 81: 305–320.

Wunderlich, S., and K. A. Gatto. 2015. "Consumer Perception of Genetically Modified Organisms and Sources of Information." *Advances in Nutrition* 6: 842–851. doi:10.3945/an.115.008870.