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THE ECONOMICS, REGULATION AND INTERNATIONAL IMPLICATIONS OF GENE DRIVES IN AGRICULTURE

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Gene drives are a class of biotechnologies with the potential to transform insect pest control in U.S. and global agriculture over coming decades. These technologies aim to permanently alter or eliminate target pest populations through the release of a relatively small number of genetically modified (GM) insects. Prototype gene drives work by using a new, low-cost method for editing genes, called CRISPR/Cas9. With this method, scientists can insert or remove genes in insects in a way that ensures that, when the GM insect mates, 100% of its offspring will inherit the target gene, creating an "evolutionary chain reaction" (see Figure 1).

Researchers are pursuing applications of gene drives to control a number of economically significant agricultural pests. These include Lepidopteran insects (among the most significant insect pests of corn, cotton, and soy, which account for over two thirds of U.S. crop value, ERS 2016), spotted wing Drosophila (one of the most significant pests of small fruit and berry producers in the U.S. with potential crop losses of $718 million annually, Bolda et al. 2010), and Asian citrus psyllid (a devastating agricultural pest with damages likely exceeding over $4 billion in Florida between 2006 and 2011, Hodges & Spreen 2012). While promising, gene drives pose significant questions for economic evaluation, risk assessment, and regulation. This edition of the *NC State Economist* discusses these issues.

Public Goods Aspects of Gene Drives and Limitations to Private Investment

The key attraction of gene drives is the possibility of permanently eliminating pest populations over wide areas. However, this source of attraction also poses challenges for commercialization. Area-wide pest control would benefit all parties in the area damaged by the pest, whether or not they paid for deployment costs. This fact, from an economist's perspective, means that gene drives have some attributes of a *public good*: Parties cannot be excluded from their benefits (or risks), and one party's benefits do not come at the cost of another's. Without institutions to incentivize cooperation, the private sector tends to underinvest in public goods, because individual firms generally cannot capture profits from the non-excludable benefits public goods generate.

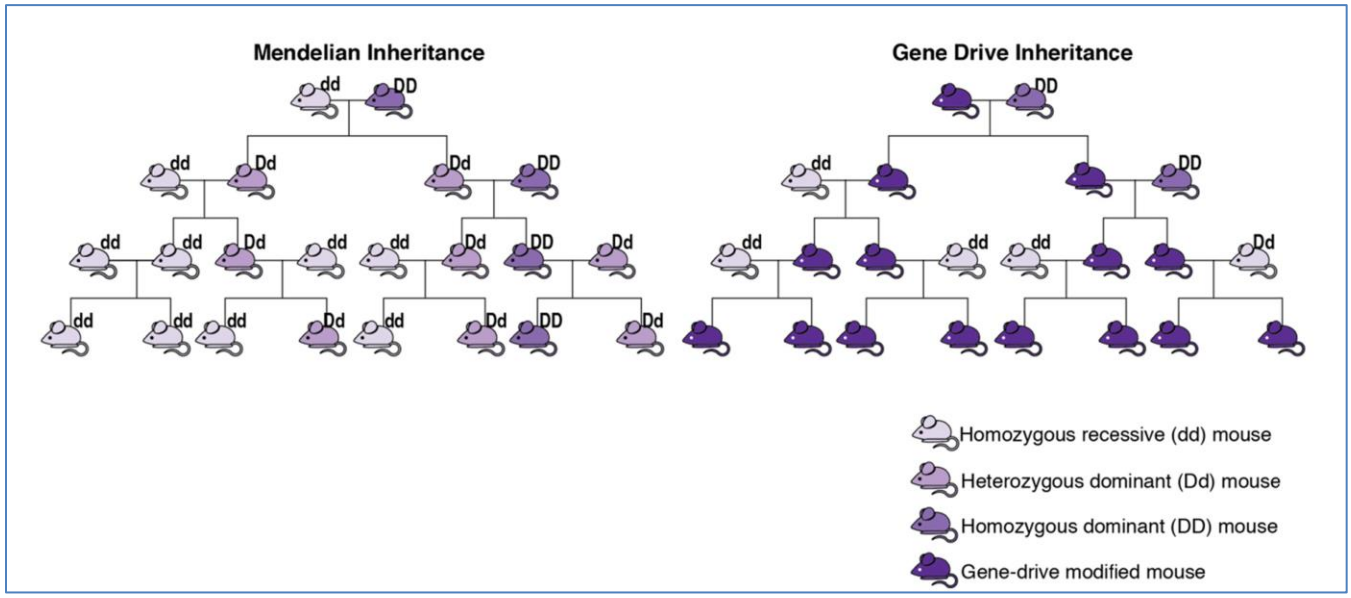

Figure 1. An illustration of gene drive compared to natural Mendelian inheritance.

This figure shows the spread of a desirable gene mutation 'D' through a population of diploid organisms (with 2 chromosomes); 'd' is the original, undesirable copy of the gene. With normal Mendelian inheritance, DD-type organisms mating with dd-type organisms produce dD-type organisms. But with gene drives, a DD-type with a gene drive will always generate DD-type offspring (also with gene drives), regardless of the mate's type. This feature means the D mutation the population can be entirely converted to DD-types from releasing only a small number of individuals initially. Adapted from NASEM (2016a, Fig. 1-2).

With gene drives, the logic of public goods suggests the bulk of research and development (R&D) in the technology will remain in the public sector. This has been the case with prior approaches to area-wide pest control techniques, including the "sterile insect technique" (SIT) and classical biocontrol. SIT consists of sterilizing pests via genetic modification or irradiation, and releasing them in large numbers to drive down the overall pest population. It differs from gene drive approaches in that population suppression via SIT may be reversed if continual releases of sterilized insects are not maintained (and hence fertile insects replace infertile ones in the population). Gene drives, in contrast, may irreversibly alter or eliminate pest populations. This irreversible, invasive potential of gene drives is shared by classical biocontrol (Hokkanen and Lynch 1995), which involves the intentional, permanent establishment of predators or parasites of a target pest (e.g. by finding and transplanting a predator from the pest's native habitat).

Gene drive releases, as with SIT and bio-control, would likely involve concentrated capital and operational costs and offer the possibility of diffuse, area-wide (or region-wide benefits). This economic structure for gene drive development makes it more likely that deployments will come from the

public rather than the private sector, as has been the case with SIT and biocontrol. A significant SIT success story—the elimination of the New World screwworm, a major pest of livestock, from North and Central America—involved substantial investment by the USDA in coordination with the governments of Mexico and Central American countries. Project expenses included construction of facilities for rearing and sterilizing screwworms, and the operational costs for running the facilities and for aerial deployments of the sterilized screwworm over wide regions. The benefits, estimated to be on the order of $800 million annually in reduced damages to U.S. agriculture, have easily exceeded these costs (Vargas-Terán 2005; Concha et al. 2006). It is difficult to imagine, given the large-scale centralized operation of this program, how private R&D investment would have been able to substitute for government investment in this case.

Risk Assessment and Regulation in the Presence of Irreversible Impacts

As with GM crops, the economics of gene drives relate to the risks they pose and how they will be regulated. In the U.S. some form of environmental or risk analysis of gene drives will be required for regulatory approval. The National Environmental Policy Act (NEPA) requires federal government actions to be reviewed for their environmental impacts. NEPA requires two levels of analysis: an environmental assessment (EA) and an environmental impact statement (EIS). Of the two, the EIS is more extensive, time-consuming and costly than an EA. The former is triggered by an EA, unless there is a "finding of no significant impact."

Whether or not an EA or an EIS will be required for gene drives will depend on the U.S. regulatory authority responsible for the specific application. In the U.S. federal government, biotechnology governance is managed under the Coordinated Framework for the Regulation of Biotechnology, which distributes regulatory responsibility among the agencies charged with implementing existing, applicable laws: the USDA, EPA and the FDA. However, the unique properties of gene drives (especially including the CRISPR-Cas9 gene editing method) obfuscate which existing laws may apply to the permitting of these technologies. Regulatory processes under the existing Coordinated Framework would therefore be determined on a permit-by-permit basis. In response to this regulatory uncertainty surrounding gene drives and other novel biotechnologies, the Coordinated Framework since 2015 has been under review for possible revision. However, no public decisions have yet been made, and regulatory uncertainty persists (Kuzma 2016).

Such regulatory uncertainty can increase private sector R&D costs. A 2016 report by the National Academies of Sciences, Engineering and Medicine (NASEM) on GM crops reported estimates from industry that commercializing a new GM crop variety can directly cost a firm at least $15 million and delay commercialization by 5-10 years, due to time involved in gathering data for submitting an application and awaiting a regulatory decision. The substantial fixed costs from regulation likely inhibit smaller, less capitalized firms from innovating in this space (NASEM 2016b, Ch. 6). In addition to the aforementioned public goods issues,

these regulatory costs further inhibit private sector incentives to invest in gene drives.

From a policy perspective these regulatory costs and delays may be justified insofar as the level of scrutiny is commensurate with the overall risks to society. Another 2016 NASEM report, on gene drives, addresses the question of risk in relation to potential benefits. Among the possible risks of gene drives raised by the report are the creation of ecological niches that could be filled by problematic competitors of the suppressed pest, as well as the possibility that the target pest evolves some form of resistance to all or part of the gene drive (NASEM 2016a). While the report did not attempt to monetize the expected benefits or risks of the technology due to its nascent stage of development, the NASEM committee recommended the use of ecological risk assessment (ERA). ERA is an approach to identifying and probabilistically quantifying the *ex ante* potential impacts of gene drive releases, including irreversible risks, prior to implementation. In economic evaluation, such risks are best weighed using the concept of option value – which accounts for the value of waiting to learn more about the benefits and risks of the technology.

Implications for Global Trade and International Treaties

The public goods and risk assessment issues with gene drives also extend to international relations. Table 1 shows a number of international treaties, standards and agreements that may be used in the international governance of gene drives. It remains to be seen how these agreements will be applied to gene drives (or whether new international agreements might be needed). Transboundary movement of GM organisms (GMOs) or so-called “Living Modified Organisms” (in the parlance of international law) has historically been managed through food safety and phytosanitary standards adopted by the World Trade Organization (WTO). The principal standard applied to GMOs is the Codex Alimentarius, issued by the Food and Agriculture Organization (FAO) and World Health Organization (WHO). The Codex Alimentarius is used by the WTO to evaluate the legality of import bans on GM food. In the case of gene drives used for agricultural pest control, the Codex Alimentarius could be used to evaluate cases where transgenic residue from an engineered insect were to be found on food.

However, because of gene drives’ special potential for direct transboundary spread, international agreements on phytosanitary standards and invasive species may also apply. The main agreement to consider in this regard is the International Plant Protection Convention (IPPC) managed by the FAO. Phytosanitary standards under the IPPC are used by the WTO. In addition to the WTO’s standards, the Convention on Biological Diversity (CBD) also has implications for how gene drives are handled under international law. While the United States has not ratified the CBD, the fact that all major trading partners with the U.S. have ratified the CBD makes it relevant to consider for U.S. agriculture. The Cartagena Protocol within the CBD is most relevant for gene drive deployment. The Cartagena Protocol issues standards and maintains a repository for LMO risk assessments through the Biosafety Clearinghouse, and addresses how damages are to be compensated with transboundary spread of LMOs.

Table 1. International agreements germane to gene drive governance

Agreement	*Relevance to Gene Drives*
FAO, WTO, WHO	
Codex Alimentarius	Establishes international food safety standards, legal justification for import bans under WTO; applied to trade in foods derived from GMOs
International Plant Protection Convention	Establishes international phytosanitary standards, legal justification for import bans under WTO; applied to plant trade and biocontrol
UNEP and the Convention on Biological Diversity	
The Cartagena Protocol on Biosafety	General agreement on safe handling, transport and use of "living modified organisms" (LMOs)

Acronyms: FAO = Food and Agriculture Organization, WTO = World Trade Organisation WHO = World Health Organisation,UNEP = United Nations Environment Program

Conclusion

Gene drives herald a radically different approach to the control of animal pests, invasive species and disease vectors. A number of scientific, economic, and social questions are intertwined in considering whether and how to adopt such an approach. Scientific questions include the technical feasibility of gene drives in terms of achieving their design objective, how the permanent removal or alteration of an entire species will affect the broader ecosystems to which they belong, as well as the feasibility of reversing alterations to ecosystems in the event of adverse ecological consequences. Economic questions concern how to weigh these uncertain benefits and risks, accounting for the possibility that the consequences of gene drive deployments may be irreversible.

The central social questions concern the relative value we place on pest and disease reduction benefits (economic or otherwise) and the possible environmental damages of gene drives.

In addition, because gene drives are intended to spread, their impacts cannot be relegated to any one area, group of stakeholders, or country. At a local and regional scale, this non-excludability of gene drive impacts suggests that public investment is critical for gene drive research into their most publically beneficial uses and

their ecological risks. Agricultural cooperatives and growers' associations also have an important role to play in supporting and monitoring gene drive deployments. At an international level, the non-excludability of impacts raises the possibility of international disputes over unilateral gene drive deployments, creating a need for effective international institutions for settling these disputes and internalizing the global consequences of countries' domestic biosafety regulations.

References

Bolda, Mark P., Rachael E. Goodhue, and Frank G. Zalom, 2010. Spotted wing drosophila: potential economic impact of a newly established pest. Giannini Foundation of Agricultural Economics, University of California, Agricultural and Resource Economics Update 13.3: 5-8. Available at: http://s.giannini.ucop.edu/uploads/giannini_public/81/fe/81feb5c9-f722-4018-85ec-64519d1bbc95/v13n3_2.pdf

Concha, C., Palavesam, A., Guerrero, F. D., Sagel, A., Li, F., Osborne, J. A., … Skoda, S., 2016. A transgenic male-only strain of the New World screwworm for an improved control program using the sterile insect technique. *BMC Biology*, 14(1), 72. http://doi.org/10.1186/s12915-016-0296-8

Economic Research Service (ERS) 2016. Crop Values: 2015 Summary. Economic Research Service, USDA. Available at: http://usda.mannlib.cornell.edu/usda/current/CropValuSu/CropValuSu-02-24-2016.pdf [accessed Dec. 14, 2016]

Hodges, A.W. and T.H. Spreen, 2012. Economic Impacts of Citrus Greening (HLB) in Florida, 2006/2007-2010/2011. University of Florida, Institute of Food and Agricultural Sciences, EDIS #FE903.

Hokkanen, H.M.T. and J. M. Lynch, eds., 1995. Biological Control: Benefits and Risks. OECD Publishing, Paris, France.

Kuzma, J., 2016. A missed opportunity for US biotechnology regulation. *Science*, 353(6305):1211-1213.

National Academies of Sciences, Engineering and Medicine (NASEM), 2016a. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. National Academies Press, Washington, DC.

National Academies of Sciences, Engineering and Medicine (NASEM), 2016b. Genetically Engineered Crops: Experiences and Prospects. National Academies Press, Washington, DC.

Vargas-Terán, M., Hofmann, H. C., & Tweddle, N. E., 2005. Impact of Screwworm Eradication Programmes Using the Sterile Insect Technique. In Sterile Insect Technique (pp. 629–650). Berlin/Heidelberg: Springer-Verlag. http://doi.org/10.1007/1-4020-4051-2_24