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Rules of the road for insect gene drive research and testing

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To the Editor

Approximately two years ago, two of us (E.B. and V.G.) demonstrated the first experimental application of CRISPR-Cas9 to 'drive' a desired trait throughout a population of fruit flies[1]. In November 2015, this same team at the University of California, San Diego, joined with A.A.J. and others at the University of California, Irvine to develop a CRISPR-based gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*[2]. A month later, a group in the United Kingdom applied a CRISPR-based gene drive to another malaria vector, *Anopheles gambiae*[3].

Many researchers around the world, including several additional authors of this Correspondence, are working to apply gene editing technologies with the hope of safely and effectively engineering populations of insects and other pest arthropods in the wild either to reduce diseases, such as malaria or dengue fever, or to control agricultural pests, such as those that transmit the bacterium that causes citrus greening disease. Important benefits could be realized if these research efforts are successful, but realizing these benefits requires sustained, open, and inclusive attention to potential environmental and social impacts and regulatory and implementation challenges. Many of these challenges were outlined in the recent report by a committee convened by the US National Academy of Sciences, Engineering, and Medicine (NASEM; Washington, DC) to review the science of gene drives and examine considerations for their responsible use[4].

In January 2016, the J. Craig Venter Institute (JCVI; La Jolla, CA) and UC San Diego convened a workshop to examine the governance challenges associated with the development and use of gene-drive modified insects. The workshop brought together leading gene-drive researchers with federal officials, ecologists, ethicists, environmental policy analysts, and others.

The meeting not only identified and discussed key challenges that scientists and decision makers will face as researchers develop gene-drive insects (and other pest arthropods, such as ticks) intended for environmental release, but also identified a series of 'action items' to help address these challenges. The resulting report[5], available online, outlines specific suggestions for researchers and research funders, US regulators and policymakers, and international organizations.

Here we focus on a subset of those action items, in particular the need for 'rules of the road'; that is, guidance documents about best practices to be followed at each stage of development of the new technology. Assembling and sharing best practices among all involved is a vital component for fostering responsible development, testing, and application of rapidly advancing technologies such as gene drives.

Gene drives are a recent advance in a long line of genetic engineering techniques, thus much of the task is not the production of guidance documents *de novo*, rather the need to update the guidance prepared for earlier generations of genetically engineered insects and other pest arthropods. Table 1 summarizes examples of important existing guidance documents, showing stage of product development (columns) and source of the guidance (rows). Underlined entries in Table 1 anticipated gene drives, although only two[4,6] directly

addressed the latest generation of CRISPR-based gene drives. Plain text entries were developed for earlier generations of genetically engineered arthropods. Many of us played key roles in the development of the listed documents; we understand first-hand the need for review and updating guidance to take into consideration these very recent advances.

Governance of rapidly emerging technologies is often best achieved by a mix of self-governance, 'soft' governance, and enforceable ('hard') governance. Guidance by professional societies and *ad hoc* groups of scientists (the top row, Table 1) provides the most nimble approach, therefore potentially the most responsive to a rapidly advancing technology, such as gene-drive modified insects[4,6–11]. At the other end of the spectrum are various forms of legal or fiduciary governance, which range from guidances (which are recommendations) to regulations and statutes, which have the force of law[12–15]. Although government guidances represent the best thoughts of the agencies at the time of issuance, these forms of governance are typically more difficult to keep current. (The table includes only guidance from US agencies, although many other nations have similar documents).

So-called 'soft governance' by regional and international organizations falls midway. These documents[16–20] provide guidance to countries, which use them as a basis for their own enforceable documents, as well as directly to product developers. Because many applications of gene-drive modified insects are intended for use in both developed and developing nations, guidance from multinational organizations plays a key role.

Given the current stage of scientific development, we believe the most pressing needs with regard to guidance are to update and develop guidance documents that could help the scientific community safely move gene drive insects and other pest arthropods from the laboratory to field trials (Table 1, middle column), starting with best practices for field trials in confined cages and then developing best practices for small-scale open field tests.

Perhaps the strongest consensus to emerge during our workshop was the importance of incorporating community engagement prior to and during approved field testing of genetically engineered insects. Technical guidance is only part of the picture. There is a critical need for guidance on best practices for community engagement, consolidating and expanding lessons learned from the case studies to date[9–11].

At the international level, the developers of these technologies strongly encouraged active engagement by the World Health Organization (WHO; Geneva, Switzerland), including an update to their existing guidance document for testing of genetically modified mosquitoes[16]. The phased testing pathway first developed in that report was extensively discussed both during our workshop and in the recent NASEM report. Although published only a few years ago, the WHO report does not directly address the latest generation of CRISPR-based gene drives. The updated framework would also be a valuable resource for international and regional organizations that focus on insect and other arthropod pests of agriculture.

The potential benefits are clear if these ongoing research efforts are successful; however, the efficacy and risks must first be carefully evaluated. To do so, we need to develop societally acceptable rules of the road.

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Table 1

Guidance documents for research on, and testing of, genetically engineered insects and other pest arthropods

Type of governance	Confined laboratory studies	Field trials (confined and staged open field)	Application and post-implementation monitoring
Self governance (e.g., guidance by professional societies or groups of scientists)	Akbari *et al.* (2015)[6] ASTMH (2003)[7]	Benedict *et al.* (2008)[8] NASEM (2016)[4] Brown *et al.* (2014)[9] Kolopak *et al.* (2015)[10] Lavery *et al.* (2010)[11]	
Soft governance (e.g., guidance by regional and international organizations and bodies)	WHO-TDR (2014)[16] NAPPO (2007)[17]	CBD (2012)[18] WHO-TDR (2014)[16] EFSA (2013)[19] NAPPO (2007)[17] WHO-VCAG (2014)[20]	CBD (2012)[18] WHO-TDR (2014)[16] EFSA (2013)[19]
Federal governance (guidance by appropriate agencies in each country, shown for U.S. only)	APHIS Guidelines (2002)[12] NIH Guidelines (2016)[13]	APHIS (2012)[14] FDA (2015)[15]	APHIS (2012)[14] FDA (2015)[15]

Note: Reports with an underline explicitly mention gene drives; those in plain text address earlier generations of genetic engineering

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