GENOME EDITING, THE BIOECONOMY, AND SECURITY

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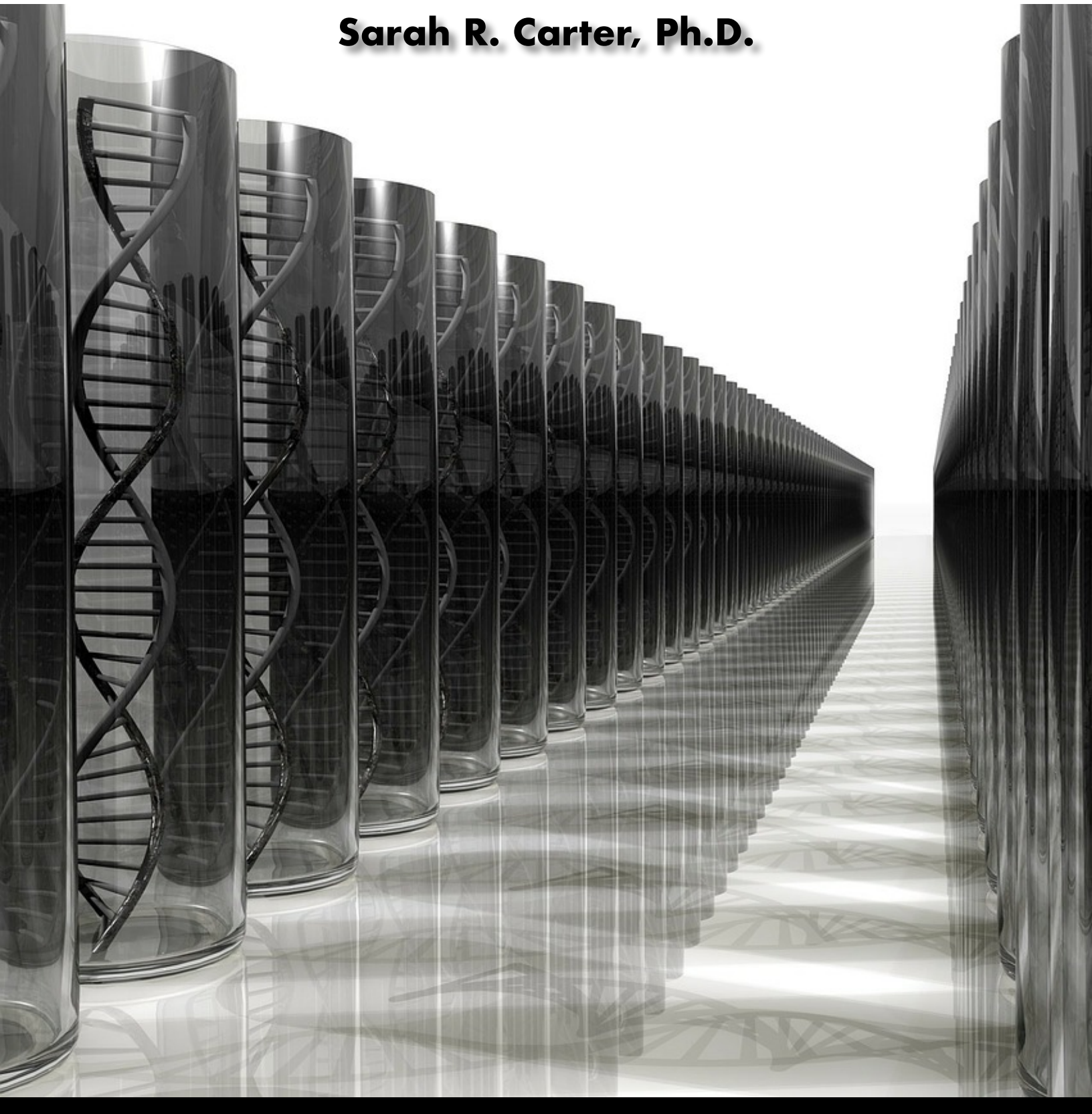

STUDY OVERVIEW

Researchers from George Mason University and Stanford University initiated a two-year multidisciplinary study, E*diting Biosecurity*, to explore critical biosecurity issues related to CRISPR and related genome editing technologies. The overarching goal of the study was to present policy options and recommendations to key stakeholders, and identify broader trends in the life sciences that may alter the security landscape. In the design of these options and recommendations, the research team focused on how to manage the often-competing demands of promoting innovation and preventing misuse, and how to adapt current, or create new, governance mechanisms to achieve these objectives.

The four study leads and seven research assistants for *Editing Biosecurity* were assisted by a core research group of fourteen subject-matter experts with backgrounds in security, the life sciences, policy, industry, and ethics. The centerpiece of the study was three invitation-only workshops that brought together the study leads and the core research group for structured discussions of the benefits, risks, and governance options for genome editing. To support these workshops and the final report, the study leads prepared two working papers on risk assessment and governance, respectively, and commissioned five issue briefs on key topics. The authors assume full responsibility for the report and any errors or omissions.

Issue Briefs and Working Papers

Perello E. *CRISPR Genome Editing: A Technical Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018.

Carter SR. *Genome Editing, the Bioeconomy, and Biosecurity*. Editing Biosecurity Issue Brief No 2. Arlington, VA: George Mason University; December 2018.

Watters K. *Genome Editing and Global Health Security*. Editing Biosecurity Issue Brief No 3. Arlington, VA: George Mason University; December 2018.

Esvelt K. *Gene Drive Technology: The Thing to Fear is Fear Itself*. Editing Biosecurity Issue Brief No 4. Arlington, VA: George Mason University; December 2018.

Vogel KM, Ouagrham-Gormley SB. Anticipating emerging biotechnology threats: A case study of CRISPR. *Politics and the Life Sciences*. 2018 Oct 23:1-7.

Koblentz GD, Kirkpatrick J, Palmer MJ, Denton SW, Tiu B, and Gloss K. *Biotechnology Risk Assessment: State of the Field*. Editing Biosecurity Working Paper No 1. Arlington, VA: George Mason University; December 2017.

Kirkpatrick J, Koblentz GD, Palmer M, Denton SW, and Tiu B, *Biotechnology Governance: Landscape and Options*. Editing Biosecurity Working Paper No. 2. Arlington, VA: George Mason University; March 2018.

All of the working papers, issue briefs, and a list of the project's participants are available at the project's website: https://editingbiosecurity.org/.

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SARAH R. CARTER BIOGRAPHY

Dr. Carter is the Principal at Science Policy Consulting LLC where she focuses on societal and policy implications of emerging biotechnologies, including issues of biosafety, biosecurity, environmental impacts, and responsible innovation.

Previously, she worked in the Policy Center of the J. Craig Venter Institute, where she led influential projects on the accelerating pace of synthetic biology and the challenges it creates for policy makers. In October, 2015, she concluded a project on the biosecurity implications of DNA synthesis with the release of "DNA Synthesis and Biosecurity: Lessons Learned and Options for the Future." Earlier, Dr. Carter led a project on the U.S. biotechnology regulatory system and the ways that synthetic biology and its applications will lead to new regulatory challenges, which resulted in the 2014 report "Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options."

In 2009–2010, Dr. Carter was a policy analyst at the White House Office of Science and Technology Policy (OSTP) where she focused on issues relating to climate change and sustainability. She is also a former AAAS Science and Technology Policy Fellow and a former Mirzayan Fellow of the National Academies. She earned her Ph.D. in Neuroscience from the University of California-San Francisco and her bachelor's degree in Biology from Duke University.

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Abstract

The landscape of genome editing technologies, capabilities, and applications is rapidly changing, which creates critical challenges in identifying and addressing biosecurity risks. The commercial opportunities for genome editing and its regulatory context will be key factors in determining how these tools are developed, disseminated, and used. This paper looks at these complex links and what they might mean for biosecurity and governance. The first section discusses commercial opportunities for genome editing with a focus on animal engineering, plant engineering, and industrial applications for engineered microbes. Therapeutic applications, though an important part of both the bioeconomy and the potential biosecurity risks that arise from genome editing, have been covered elsewhere and are discussed only briefly. The second section discusses the regulatory context in the U.S. for genome editing applications. Some genome edited products (e.g. many plants) are unlikely to be regulated in the same way as earlier generations of biotechnology, while there is a great deal of uncertainty for other products (e.g. many animals). The regulatory process has played an important role in the shape of the biotechnology industry to date, and recent developments could have major implications for how products are pursued (and by whom) in the future. The last section discusses some of the biosecurity and governance challenges that arise from the use of genome editing. The widespread and diffuse nature of the technology and how it is used will make it difficult to identify, scope, and prioritize biosecurity risks that deserve attention. To be successful, governance mechanisms must rely on the community (including researchers, industry, and broader scientific stakeholders) in their development and implementation.

Commercial Opportunities for Genome Editing

It has been estimated that, in 2014, the genome editing market was worth nearly $2 billion, and is expected to double by 2019, with the number of patents filed for CRISPR-based technologies increasing exponentially (Brinegar, *et al*., 2017). Although it is difficult to obtain reliable economic numbers specific to genome editing, estimates for all biotechnologies (approximately $324 billion in total for 2012) indicate that, in 2012, about 28% of revenues were for therapeutics and nearly 40% were for genetically engineered (GE) crops, with industrial products making up the difference (Carlson, 2016). For genome editing, all signs point to a rapid acceleration of technical capability, economic investment, and product development.

There are clear human therapeutic applications for genome editing, with at least two recent products already in the clinic from Sangamo Biosciences (Kaiser, 2017). A wide range of somatic (non-heritable) genome editing products is likely to follow (e.g., Bagley, 2018), with complex patenting arrangements underscoring their anticipated value (Brinegar, *et al*., 2017; SynBioBeta, 2016a). This industry, and the wide range of basic science that supports it, relies on the availability of tools and platforms that are constantly under development. There are many companies and other entities that provide genome editing (especially CRISPR) constructs,

reagents, and tools. Many laboratories are working to improve CRISPR-based systems by, for example, reducing off-target edits, and many of these new tools and techniques are rapidly shared. Some CRISPR constructs can be ordered already packaged in a variety of vectors for easy transfection of cells or even *in vivo* delivery to different mammalian tissues. Even so, there is a strong market for improved vectors that would provide more specific or efficacious targeting and/or fewer side effects; advanced lipid nanoparticles are one promising approach (e.g. from Arcturus or Acuitas). This flurry of activity in advanced capabilities for human therapeutics drives a lot of the discussion of genome editing and its potential impacts, including in discussions of biosecurity. However, there are other areas where genome editing may also have significant economic impacts.

Animal engineering is one area where genome editing is likely to play a major role. In the near future, a wide range of new insect applications is likely to become available, including for pest control and agricultural purposes.[1] CRISPR-based tools will also allow for easier editing of mammalian genomes, with most applications focusing on germline (heritable) edits (Cohen, 2016; Telugu, *et al*., 2017). Several genome editing applications have already been demonstrated, including cattle that are hornless (Carlson, *et al*., 2016), tuberculosis-resistant (Gao, *et al*., 2017), or pass on only male (fast-growing) traits (Rosenblum, 2018). Pigs have been edited to be resistant to porcine reproductive and respiratory syndrome (Brouillette, 2016; Whitworth, *et al*., 2016), and to have humanized organs for transplantation into humans (Reardon, 2015; Lash, 2017). Breeders have also expressed interest in CRISPR-based genome editing in dogs to address common in-bred health disorders (Rosenblum, 2017), and in horses for increased speed and stamina (Basu, 2018).

The availability and capabilities of *in vitro* fertilization facilities may impact how commonly and by whom genome editing is used in animals. Cattle breeders are increasingly adopting *in vitro* fertilization techniques (Archibald and Stanheim, 2015), with some companies now offering *in vitro* fertilization along with embryo micromanipulation and other tools that would allow easy genome editing (e.g OvaGenix). *In vitro* fertilization is less common for pigs, but genome editing techniques for these animals are being rapidly developed. In addition to being used for humanized organs or for food, pigs are an important model system for studying cardiovascular and other diseases in humans. Advances made in genome editing techniques in pigs (including *in vitro* fertilization techniques) may also inform the procedure in humans (Krummerer, 2017). As these techniques and capabilities become more available and easier to use, the possibilities for genome editing in mammals, including humans, will expand.

Genome editing has also made an impact in plant engineering, including easier and more efficient editing of a wider range of plants (Altpeter, *et al*., 2016; Borel, 2016). These applications have clear economic implications, with opportunities for crop improvement (e.g. drought tolerance, pest resistance, higher yields) a major driver. As mentioned above, GE crops

[1] Some of these products are likely to contain gene drive constructs. This document excludes discussion of gene drive-based applications because they are discussed in other project Issue Briefs.

are already a major industry, with $128 billion in revenues in 2012 (Carlson, 2016). A lack of regulatory oversight by USDA for many genome edited plants is also pushing development of genome editing tools over traditional transgene-based products (Kubis, 2016). In addition to near-term, direct applications, CRISPR also has the potential to greatly expand basic knowledge about the links between genotype and phenotype in plants. Previously, studies largely depended on mutagenized plants or transposon libraries, which have to be bred for many generations to reliably isolate a gene or mutation of interest. Multigenic traits (those that depend on multiple genes) have been particularly challenging to study. Improved knowledge of this basic biology is likely to expand the types of traits that can be engineered.

However, there are several technical challenges to using genome editing tools in plants, with transformation of plants a key bottleneck. The use of *Agrobacteria* for transfer of DNA into plants has been a primary method of transformation for 30 years, and most CRISPR-based genome editing in plants still relies on this method.[2] There has been renewed interest in developing new methods for transformation, including by the National Science Foundation (NSF, 2016) and in the private sector. For example, scientists are currently exploring ways to apply CRISPR/Cas9 constructs to plant cells without the need for expression from DNA. Additional challenges with working with plants will also need to be overcome before the potential of CRISPR-based genome editing will be fully realized. Highly repetitive DNA sequences and polyploidy (i.e. having more than two copies of each chromosome) are common in many plants, making it difficult to ensure that a CRISPR construct has edited all targets without off-target edits. Also, many plant species depend heavily on non-homologous end-joining to address double-stranded breaks in DNA rather than homology-directed repair, which makes CRISPR-mediated disruption of genes reliable, but insertion of desired DNA difficult. To date, only well-resourced labs have been able to accomplish knock-in of DNA sequences using CRISPR-based methods (e.g. Shi, *et al*., 2017; Wang, *et al*., 2017).

In recent years, there has been a high level of economic activity and investment in advanced biotechnologies that depend on engineering of bacteria and yeast. Applications include microbial products that produce compounds such as fuels, pharmaceuticals, fragrances, advanced materials, and other high-value products (e.g. Amyris, Synthetic Genomics). Other companies are developing microbes that could be directly applied in the environment for bioremediation, biomining, or crop nutrition (e.g. Pivot Bio). Engineered microbes for health applications, such as engineered gut microbes to address metabolic disorders (e.g. Synlogic), are moving forward.

For many microbial applications, CRISPR-based genome editing may be helpful, but is just one tool among many that have been developed for engineering microbes. The declining cost of synthetic DNA is much more fundamental to the success of these companies. Ginkgo

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[2] Plant developers use *Agrobacteria* to insert a CRISPR construct (DNA encoding Cas9 plus gRNA) into the genome of the plant (e.g. Wang, *et al*., 2017). Once the CRISPR construct has been expressed and has edited its target sequence in the plant genome, remaining *Agrobacteria* DNA as well as the CRISPR construct can be bred out of the final product, leaving only the targeted edit. Such a product would not be regulated by USDA (see below).

Bioworks, a company that engineers microbes to produce a wide range of biological compounds, recently bought Gen9, a leading DNA synthesis company, showing the integral relationship between microbial engineering and DNA synthesis (Gen9, 2017). In addition to cheap DNA, advances in robotics and bioinformatics are also driving advances in the field (SynBioBeta, 2016b). Companies that work primarily with yeast rather than bacteria may see a bigger role for CRISPR-based genome editing because yeast have larger, more complex genomes and more efficiently repair Cas9-mediated double-stranded DNA breaks. Amyris, a leading company that works with yeast, and others are using CRISPR in their engineering processes (Chatsko, 2015; GenomeWeb, 2016). CRISPR is likely to be most helpful to companies that are trying to engineer species that are not traditionally used in the laboratory, where other engineering techniques may not be as reliable, including many microbes designed to persist in the environment or in natural microbial communities.

Regulatory Context for Advanced Biotechnology

The links between commercial opportunities in biotechnology and security considerations are complex. Most fundamentally, the bioeconomy plays a key role in the economic competitiveness of the U.S. Already, concerns have been raised that China is taking the lead in CRISPR-based therapeutics (Rana, *et al*., 2018), though it continues to lag behind the U.S. in agricultural biotechnology (Yan, 2018). In addition to economic advantages, maintaining leadership in the bioeconomy will allow the U.S. to set global norms and expectations for pursuing new products ethically, safely, and securely (Gronvall, 2015). Even within the U.S., the regulatory environment will play a key role in how different genome editing technologies are pursued. It will impact how and by whom genome editing tools are developed and how powerful those tools are likely to be. It will also determine how widely the knowledge and capability to engineer organisms, including mammals, will be disseminated. Nefarious actors are not likely to abide by the regulatory system, but the commercial and regulatory environment will help determine their access to tools and resources.

In the U.S., biotechnology products are regulated under the Coordinated Framework for the Regulation of Biotechnology, first developed in 1986 and revisited in 2016–2017 (OSTP, 1986; OSTP, 2017). A key principle of the Coordinated Framework is that biotechnology products are regulated under different regulatory authorities depending on the type of product it is rather than how it was made. Each of the regulatory agencies (FDA, EPA, and USDA) have purview over different types of products and have their own set of regulations and guidance specific to GE products within that purview, as described below. As a result, the system acts as a patchwork of oversight with different definitions, regulatory triggers, procedures, assessments, and approval (or deregulation) pathways. The complexity of the system and the potential for similar products to be treated differently has been frequently cited as problematic (NASEM, 2017a; Carter and Friedman, 2016). Furthermore, recent advances in biotechnology techniques and the increased pace of biotechnology product development create significant challenges for

the regulatory system (NASEM, 2017a; Carter *et al*., 2014). Despite these challenges, the regulatory system will play a key role in how biotechnology products are developed and pursued commercially in the U.S.

FDA's oversight of human drugs and medical devices is comprehensive and there is no ambiguity about its role in regulating genome editing therapies in humans. Currently, only somatic therapies are considered by FDA, and there has been much discussion of how germline editing might be addressed (NASEM, 2017b). Chinese researchers have already used CRISPR to edit human embryo DNA, though therapeutic germline edits remain untested (Tang, *et al*., 2017). If and when FDA begins to consider human germline editing products, a wider range of technical tools and approaches for doing so is likely to follow.

Beyond FDA's oversight of human drugs and medical devices, the use of genome editing may yield products that increasingly fall outside of the U.S. biotechnology regulatory system. For animals engineered using genome editing, there are a number of uncertainties about how they will be regulated. Previous guidance from FDA indicated that a gene inserted into the genome of an animal and the resulting gene product constituted animal drugs, but the guidance did not anticipate genome editing techniques that result in small changes in the DNA such as point mutations. In January 2017, FDA released draft guidance for public comment that indicated that the agency might oversee animals that have been engineered using genome editing techniques (FDA, 2017b), and this stance was recently reaffirmed by FDA commissioner Scott Gottlieb (FDA 2018). The draft guidance has not been finalized, and some product developers have spoken out against such oversight by FDA, arguing that single point mutations could occur naturally and should not be subject to rigorous assessment and regulation (Zhang, 2017). Many in the industry are awaiting clarification from FDA on what this regulatory process will entail.

FDA's oversight excludes insect plant pests, which are regulated by USDA. Another potential exception from FDA regulations is GE animals intended to be used to decrease a pest population, which could be regulated by EPA under their pesticide provisions. FDA and EPA finalized Guidance #236 in September 2017 (FDA, 2017c), which states that mosquitoes used for population suppression will be regulated by EPA while those with a human health-related claim will be regulated by FDA. Although the guidance is specific to mosquito-related products, such an approach could also be used for other products (e.g. GE mice used for control of invasive mouse populations).

USDA regulates insect plant pests and GE plants based on the Plant Protection Act, which gives the agency authority to regulate plant pests. Recent plant genetic engineering techniques, including genome editing, have allowed product developers to avoid the use of plant pests and DNA sequences derived from plant pests in their final plant products, and so avoid regulatory oversight (Carter, *et al*., 2014). This system is already encouraging plant product developers to pursue these newer techniques, including CRISPR-based genome editing, rather than more traditional genetic engineering (for examples, see USDA, 2018). USDA has indicated that it will not issue new regulations in the near future that capture genome editing, leaving many

modern plant biotechnologies unregulated by USDA (though plants used as food are still subject to some oversight by FDA).[3] Regulatory oversight in other countries, particularly Europe, has been less permissive than in the U.S. for traditional GE plants, and genome editing will likely fall under the same rules as those earlier plants (Kupferschmidt, 2018).

To date, plant engineering has been dominated by large corporations, primarily in the U.S., engineering crops that are grown at large scales. Development costs (including regulatory costs) have been prohibitive for smaller developers and for less profitable crops (NASEM, 2016). Genome editing tools will decrease these costs, allowing a wider range of actors to develop new products. As tools and techniques for plant transformation become simpler and more accessible (although still a major bottleneck, as discussed above), plant engineering will further expand, and will likely be applied to a wider range of plants. Already, plant engineering that avoids regulation has been pursued by small start-up companies (e.g. TAXA, which makes fragrant moss as a household product).

Investments in genome editing tools, decreased costs for engineering and development, and decentralization of engineering capabilities will expand the types of products that are developed and the actors that can develop them. For plant and animal products, opportunities to develop and market many products in the U.S. with limited regulatory oversight could be transformative, though it is unclear if and how quickly society will embrace these possibilities. The increasingly wide range of individuals, companies, and other entities capable of genome editing, and the tools that are developed to support them, may have implications for biosecurity (NASEM, 2018).

Biosecurity and Governance

Many biosecurity risks related to genome editing arise in the context of research tools that may be used to harm humans. Tools and resources for genome editing, including research constructs and vectors, have become their own industry. The open source nature of the life sciences as practiced today ensures that many novel capabilities are rapidly shared. For example, Addgene is a non-profit repository of research tools, and has a stated purpose of accelerating research and discovery by improving access to these materials (Joung, *et al*., 2015). It currently offers a wide range of CRISPR constructs, as well as adeno-associated viral vectors that it advertises as suitable for *in vivo* use in mammals (as well as plant vectors for different types of plants). A wide range of companies that provide laboratory research reagents now sell genome editing tools, including CRISPR constructs already packaged in a variety of vectors for different purposes.

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[3] Plants intended to be used as a food are still expected to comply with FDA's voluntary assessment process for GE foods, which addresses potential risks to human health (but not potential impacts on the environment). In January 2017, FDA released a request for public comment on genome editing in plant varieties used as food (FDA, 2017a), but no new guidance has yet been released.

Although there would be some hurdles to someone trying to use genome editing tools for nefarious purposes, the rapid pace of development and dissemination of these tools deserves closer scrutiny. Currently, genome editing tools are not subject to any regulatory oversight unless and until they are used to edit humans (or animals; see above). Guidance related to biosecurity measures for these technologies has not been provided by the U.S. government, industry, or outside groups.[4]

Advances in the field of genome editing in animals, particularly mammals, for commercial purposes may also affect the possibilities for genome editing in humans. Although most product development for therapeutic purposes in humans is focused on somatic applications, genome editing in non-human mammals is focused on germline editing. CRISPR in particular has made germline engineering far easier (Cohen, 2016; Telugu, 2017). As mentioned above, advances in *in vitro* fertilization availability and capabilities for animal genome editing are expanding, increasing the variety of applications and actors that may pursue it. This expansion will be accelerated if FDA limits its regulatory oversight of genome edited animals. For legitimate animal products, potential off-target edits, hetero- or homozygosity (whether an edit was made on one or both chromosomes), and mosaicism (whether only a fraction of cells contain edited DNA) would likely be evaluated and, if necessary, addressed (such measures would be required by FDA, if it claims regulatory oversight). However, such issues may not deter someone with less concern about the well-being of the resulting animal.

Scenarios related to the nefarious use or misuse of genome editing in plants are less defined and further into the future. The current agricultural industry in the U.S. is dominated by large companies that have wide geographical reach and strong economic incentives to know and control the genetic content of the seeds that are being planted. Subverting this system using genome editing in plants (e.g. to make cotton more susceptible to pests or corn that expresses a toxin) is difficult to envision, even when technical hurdles, as discussed above, are cleared. When genome editing in plants is more routine, and so more available to small-scale product developers, farmers, and hobbyists, it is possible that it could be misused, but its impacts may be limited. A more likely biosecurity risk to agricultural systems from genome editing may be from insect pests that contain novel traits (e.g. pests with resistance to pesticides).

Governance of genome editing technologies will be challenging. Discussions with a wide range of actors in the advanced biotechnology community, including industry, non-profit entities such as Addgene, and researchers, would be extremely valuable for brainstorming appropriate biosecurity measures as well as understanding the nature of the risk. In the absence of meaningful engagement, it may be premature to discuss appropriate governance options to address potential biosecurity concerns that arise from genome editing. The most effective

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[4] U.S. government activity on the issue of biosecurity has focused on pathogen research, including regulations and policies for Select Agents, Dual Use Research of Concern (DURC), and Potential Pandemic Pathogens (PPP).

measures will be those that are recognized by the affected community as necessary and reasonable in light of widely perceived risks. Regulatory (legally binding) approaches to these issues would be very difficult to develop, burdensome to the industry, and ultimately counterproductive.

One governance model that may be relevant is the 2010 HHS Screening Framework Guidance for Providers of Synthetic Double-stranded DNA. The largest DNA synthesis companies in the U.S. (and some in other countries) are members of the International Gene Synthesis Consortium (IGSC), which follows screening practices in voluntary compliance with the HHS Screening Framework Guidance. The Guidance is non-regulatory, but calls on DNA synthesis companies to screen their customers and the sequences of DNA that are ordered to ensure that pathogenic DNA (i.e. DNA sequences that match DNA sequences from a Select Agent) is only sold to individuals with a legitimate reason to have it. The IGSC estimates that, collectively, its members represent about 80% of the global market for double-stranded DNA. Many companies outside the IGSC also practice some type of customer and/or sequence screening procedures (Carter and Friedman, 2015).[5]

The screening framework adopted by the IGSC was first discussed among the DNA synthesis companies before the HHS Screening Framework Guidance was finalized. The companies were aware that the U.S. government was developing the guidance, but they also recognized that their long-term sustainability depended on their due diligence; it was in their self-interest to ensure that their products were not used for nefarious purposes. It is possible that companies currently conducting genome editing and/or providing genome editing tools may come to a similar conclusion if opportunities for engagement on the topic of biosecurity were more available.

Currently, it is not clear that the genome editing community has fully considered potential misuse of their products. Discussions of the broader implications of genome editing usually focus on ethical issues that arise from germline editing of humans (e.g. at CRISPRcon; Davies, 2017), while discussions of biosecurity in the broader synthetic biology community are dominated by the possibility of *de novo* synthesis of pathogens (e.g. at SB7.0; van der Helm, 2017). The U.S. government and other funders could help seed more productive conversations.

A key starting point for these conversations should be defining what risks should be addressed. For the HHS Screening Framework Guidance, that work had already been done: the Select Agent Regulations had already set a legal standard that access to a specific set of listed pathogens should be restricted. Genome editing risks are more diffuse; generating a workable

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[5] The widespread, voluntary adoption of this Guidance likely provides some level of biosecurity, but it does not fully address the issue. Researchers can, with some additional effort and expertise, synthesize pathogenic DNA themselves or assemble it from oligonucleotides (short, single-stranded DNA that is not screened). Furthermore, the rapidly declining cost of DNA synthesis puts pressure on DNA synthesis companies to abandon their relatively expensive screening procedures. Options to help support the DNA screening framework into the future have been discussed previously (Carter and Friedman, 2015; DiEuliis, *et al*., 2017).

consensus on this point has been difficult even in small discussions among biosecurity professionals.

If and when a range of risks is defined, then a collaborative process can be used to identify bottlenecks in realizing those risks and options for governance to address them (see, for example, Garfinkel, *et al*., 2007). It will be critical to ensure that multiple stakeholders are included in discussions so that potential impacts on a wide range of factors, including scientific and economic advancement, are fully understood. Once the options have been discussed, researchers, companies, and the broader scientific community will need to take the lead to determine what option or options to pursue, with the U.S. government playing a supporting role, if any.

The rapid pace of change in the genome editing enterprise will be a key challenge for effective governance (NASEM, 2017a; NASEM, 2018). During the course of a two-year process for policy development, not only will the science and capabilities be significantly advanced, but the shape of the industry may be different, with new advances driving new investments. It may not be possible to create a future-proof framework, but a successful one should be adaptable to a range of biosecurity risks, agnostic to the specific type of tools used, and frequently revisited. It will take significant commitment and creativity to develop and implement such a system.

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