

Editing Biosecurity:

Needs and Strategies for Governing Genome Editing

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STUDY OVERVIEW

In 2017, researchers from George Mason University and Stanford University initiated a two-year multidisciplinary study, *Editing Biosecurity*, to explore critical biosecurity issues related to CRISPR and related genome editing technologies. The overarching goal of the study was to present governance options and recommendations to key stakeholders, and to identify broader trends in the life sciences that may alter the security landscape. In characterizing the landscape, and 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.

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This report is open for peer review and comment until December 31, 2018. All comments can be sent to: editingbioproject@gmail.com. Following incorporation of peer review comments, a final version will be released in January 2019.

The views and opinions expressed in this report are those of the authors. They do not represent their institutions, nor do they represent the views of the workshop participants, or the organization that funded the study. 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 and 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.

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Vogel KM, Ouaghram-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. *Biotechnology Governance: Landscape and Options*. Editing Biosecurity Working Paper No 2. Arlington, VA: George Mason University; March 2018.

The working papers and issue briefs are available at the project's website:

<https://editingbiosecurity.org/>

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Editing Biosecurity: Needs and Strategies for Governing Genome Editing

Genome editing has the potential to improve the human condition.

- Genome editing is poised to make major beneficial contributions to basic research, medicine, public health, agriculture, and the biomanufacturing industry that could reduce suffering, strengthen food security, and protect the environment.

Genome editing is disruptive to the biosecurity landscape.

- The threat landscape may expand to include new means of disrupting or manipulating biological systems and processes in humans, plants, and animals.
- Genome editing could be used to create new types of biological weapons.
- The “democratization of biotechnology” may dramatically increase the number and type of individuals and groups capable of misusing genome editing.

CRISPR illuminates broader trends and the challenges of an evolving security landscape.

- Scientific, technological, economic, and social trends are increasing the range of potential biological hazards, diversifying the sources of these hazards, multiplying the routes of exposure, expanding the populations that may be exposed, and increasing the population’s level of susceptibility. An approach to biosecurity that accounts for these trends, and encompasses risks posed by deliberate, accidental, and reckless misuse, can help navigate the complex and evolving security landscape.

Take the technology seriously.

- A thorough, informed, and accessible analysis of any emerging technology is crucial to considering the impact that it may have on the security landscape.

Key stakeholders must be engaged.

- Stakeholders in the genome editing field encompass a more diverse array of actors than those involved in previous biosecurity discussions. The engagement of new communities of actors is required.

Applied research is needed to create and implement innovative and effective policies.

- Applied research is necessary to continue the process of modifying existing governance measures, and adapting new ones, as new genome editing technologies and applications are developed, new stakeholders emerge, and new pathways for misuse are identified.

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EXECUTIVE SUMMARY

Study Approach

This study's purpose was to highlight the changing safety and security landscape engendered by the emergence of new genome editing technologies, help policy-makers and other stakeholders navigate this space, and illuminate broader trends in the life sciences that may impact the biosecurity landscape.

The two-year *Editing Biosecurity* study was led by four researchers from George Mason University and Stanford University. 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. The study leads and research assistants prepared two working papers to frame the workshop discussions. The first working paper reviewed past studies that assessed the risks posed by emerging dual-use technologies. The goal of this working paper was to provide a baseline for understanding the security implications of genome editing and to identify best practices in risk assessment. The second working paper provided an overview of the current governance landscape for biotechnology and a framework for evaluating governance measures. Each workshop included a range of scientific, policy, ethics, and security experts. The study leads gathered additional information from subject-matter experts in the form of five commissioned issue briefs. Several of the study's experts served as discussants who critically engaged the content of the issue briefs through iterative commentary and feedback.

The study leads and core research group have backgrounds in various disciplines, including the life sciences, social sciences, and the humanities, an approach designed to ensure a rigorous research process underpinned by the inclusion of a variety of perspectives, and further complemented by numerous areas of expertise. The study and its products relied on unclassified, open, and publicly accessible information. The study was an independent academic work in which the charge and scope were determined by the research team. In combination, these factors were motivated by the team's goal of producing open and accessible research outputs that can assist stakeholders in crafting more effective and informed policies.

Introduction

In 2012 scientists discovered that an obscure bacterial defense mechanism called Clustered Regularly Interspaced Short Palindromic Repeats (**CRISPR**) could be used more widely to make precise cuts in DNA. Less than a year later, CRISPR was used to edit the genome of mammalian cells. In combination, these two developments launched a revolution in the field of genome editing that has transformed the life sciences research enterprise.

While the capability to modify the genomes of living organisms is over four decades old, CRISPR is the most significant recent advance and most publicly visible example of genome editing technology. CRISPR allows scientists to add, delete, or modify multiple genes simultaneously with a high degree of precision. Genome editing is poised to make major contributions to basic research, medicine, public health, agriculture, and the biomanufacturing industry, thereby reducing widespread suffering and improving the human condition.

There are risks associated with intentional, reckless, or accidental misuse of genome editing. Genome editing enables new discoveries about how microbes, humans, animals, and plants work, and it provides new tools for manipulating these biological processes. As a result, the threat landscape may be expanded to include new means of disrupting or manipulating biological systems and processes in humans, plants, and animals that are in addition to future threats coming from edited pathogens. The number of potential vectors, targets, and effects will grow rapidly as genome editing is used to explore and exploit biology. Genome editing could be used to create new types of biological weapons, such as those able to target the microbiome and the immune and nervous systems. Further, the “democratization of biotechnology” may dramatically increase the number and type of individuals and groups capable of misusing genome editing. In effect, the versatility, flexibility, and precision offered by new genome editing techniques, such as CRISPR, increases the attack surface, which encompasses the number, accessibility, and severity of vulnerabilities that could be exploited to cause harm, either deliberately, accidentally, or recklessly.

As the biotechnology landscape evolves, so too will the attack surface.

Genome Editing

Genome editing has emerged as a lively discipline of genetic engineering, making use of successive generations of increasingly simple and flexible tools that allow a modern molecular biologist to perform an almost unlimited range of alterations to the genomic makeup of an organism.

One can view genome editing from four perspectives.

- Genome editing **tools** are the specific molecular methods that are used to alter an organism's DNA. They may be used in conjunction with other tools, and as part of larger processes. The most well-known of these tools is called CRISPR.
- Genome editing **capabilities** refer to the molecular alterations and outcomes that these tools allow scientists to achieve.
- Genome editing **processes** are the technologies and procedures, not limited to the genome editing tools themselves, that are essential for planning, executing, and measuring the outcome of a genome editing activity.
- The genome editing **field** comprises the entire set of activities, technologies, cultural norms, economics, and ecosystems of developers and users associated with these techniques.

Box 1. Four perspectives from which to view genome editing.

Genome editing tools are typically composed of three components: the payload, the guidance module, and the delivery system. The payload is a nuclease protein that can cut DNA or RNA, effectively removing or crippling a specific gene in an organism. Additional protein, DNA, or RNA can be added to the payload to insert new DNA at a cut site, or modulate the expression of a specific gene. The payload is guided to its target by either a customized binding domain or, in the case of CRISPR, guide RNAs—programmable elements that act as a guidance molecule. Finally, these components are assembled and delivered into cells using a genome editing vector.

CRISPR

CRISPR is the most significant recent advance and most publicly visible example of precision genome editing technology.

CRISPR allows scientists to add, delete, or modify multiple genes simultaneously, and with a high degree of precision. Consequently, CRISPR has launched a revolution in the field of genome editing that is having a transformative effect on the entire life sciences research enterprise.

How CRISPR Works

The introduction of CRISPR as a genome engineering technique occurred between 2012 and 2013. CRISPR-Cas9 was the first in a rapidly expanding suite of RNA-guided endonuclease (RGEN) tools. The core of the CRISPR RGEN system (see Figure A) is a CRISPR-associated or Cas nuclease protein, with multiple functions, one of which is to bind to nucleic acids (double-stranded DNA, in the case of Cas9), unwind it, and introduce a break at a target site. A guide RNA binds to the Cas protein and provides a molecular targeting function, which can be programmed to ensure the nuclease cuts at the intended target. The operation to assemble a new CRISPR RGEN that is suitable for use in a cell can be as short as a few hours to days. CRISPR can be delivered via numerous types of vectors including plasmids, messenger RNA, viruses, and synthetic ribonucleoproteins. The major drawback associated with CRISPR is its lower level of specificity resulting in a higher likelihood of off-target effects compared to other genome editing tools, although this depends on the specific combination of editors and targets. However, this drawback is largely offset by the relative simplicity of the CRISPR system.

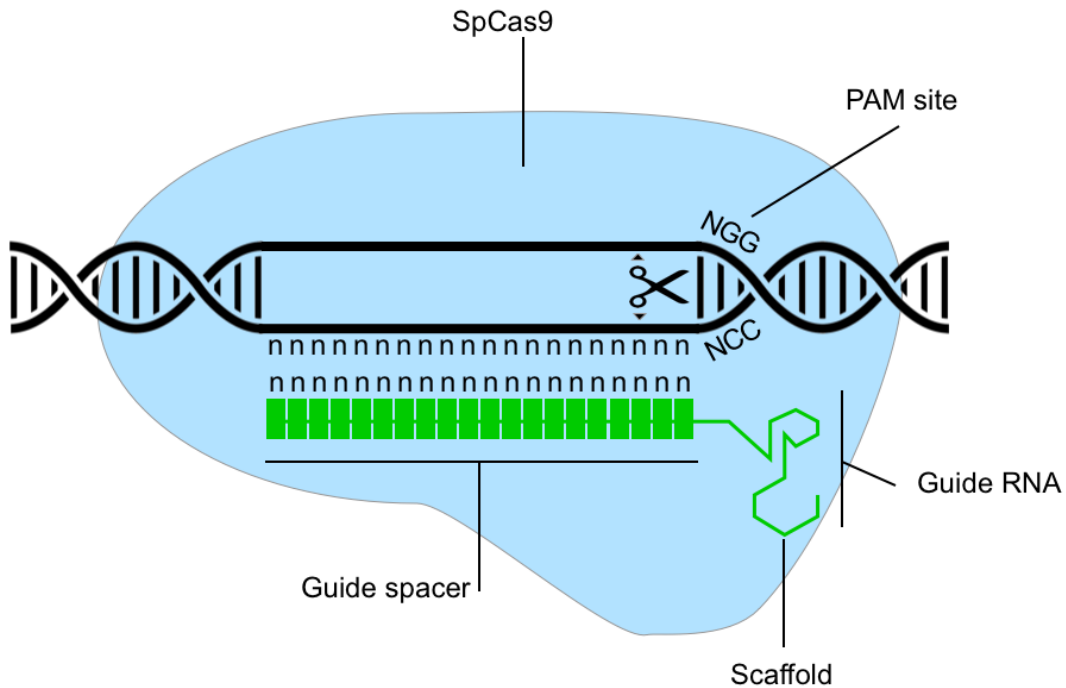


Figure A. The Cas9 nuclease unwinds double-stranded genomic DNA at a PAM site—a specific DNA motif with an NGG sequence—and cuts at the site where guide RNA spacer matches one strand of the DNA. Source: Adapted from Figure E in Perello E. CRISPR Genome Editing: A Technical Policy Primer. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

CRISPR has been compared to a Swiss Army knife because of its versatility in applications. Yet genome editing with CRISPR is not simply the act of cutting and repairing the target DNA. It includes several events leading up to, and beyond, those moments. Genome editing is thus not a discrete activity, but rather a generalizable process.

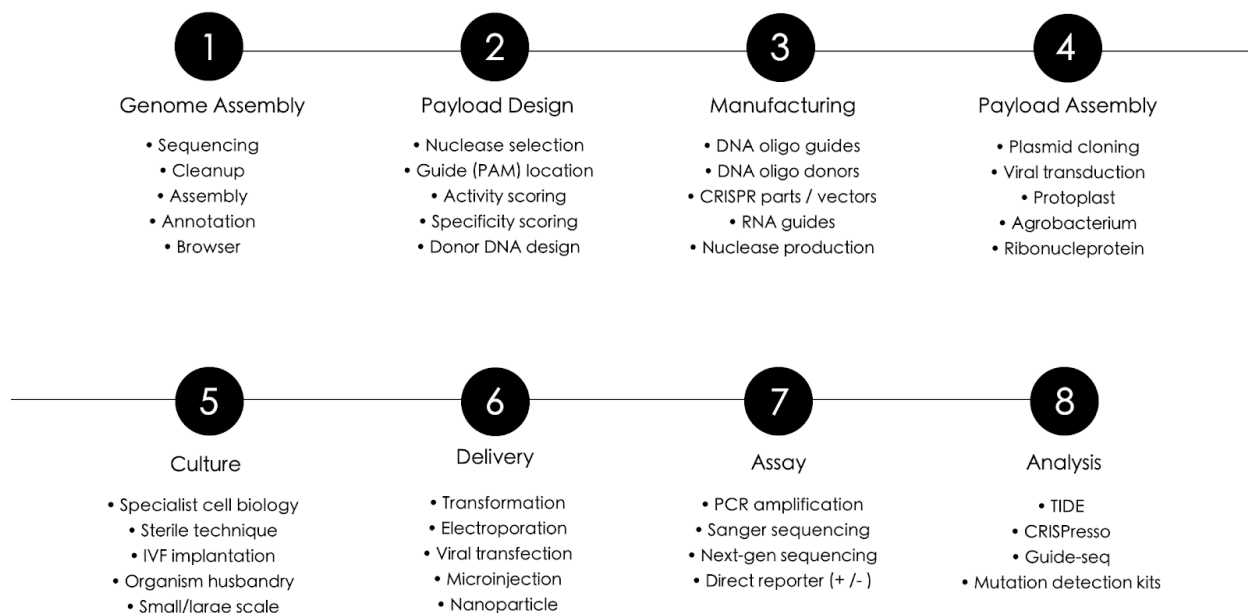


Figure B. An idealized CRISPR process with each step representing a distinct component of a typical genome editing experiment. Source: Figure M in Perello E. *CRISPR Genome Editing: A Technical and Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Many variants of the generalized genome editing process exist to meet different technical or experimental goals. Successful execution of each step can be challenging without the correct skills, and to this extent, CRISPR technology users must be familiar with a distinct range of laboratory tools and techniques, be comfortable using molecular tools and delivery techniques, maintaining viable cells or organisms over extended timeframes, and using various assays, bioinformatic design tools, or analysis packages. The connection of steps within the entire genome editing process is not always a simple affair, and a user may encounter problems that will need to be troubleshoot. Depending on project complexity, either an individual or a team will take on one or more of these steps, each requiring some specialist training and technology access.

The Benefits and Risks of Genome Editing

Benefits

Genome editing is a powerful technology that promises a wide range of benefits across a number of domains, but there are technical and social obstacles to realizing these benefits. Over the long-term this realization will also depend on society's ability to facilitate beneficial research and prevent, or if necessary mitigate, the potential risks posed by the technology.

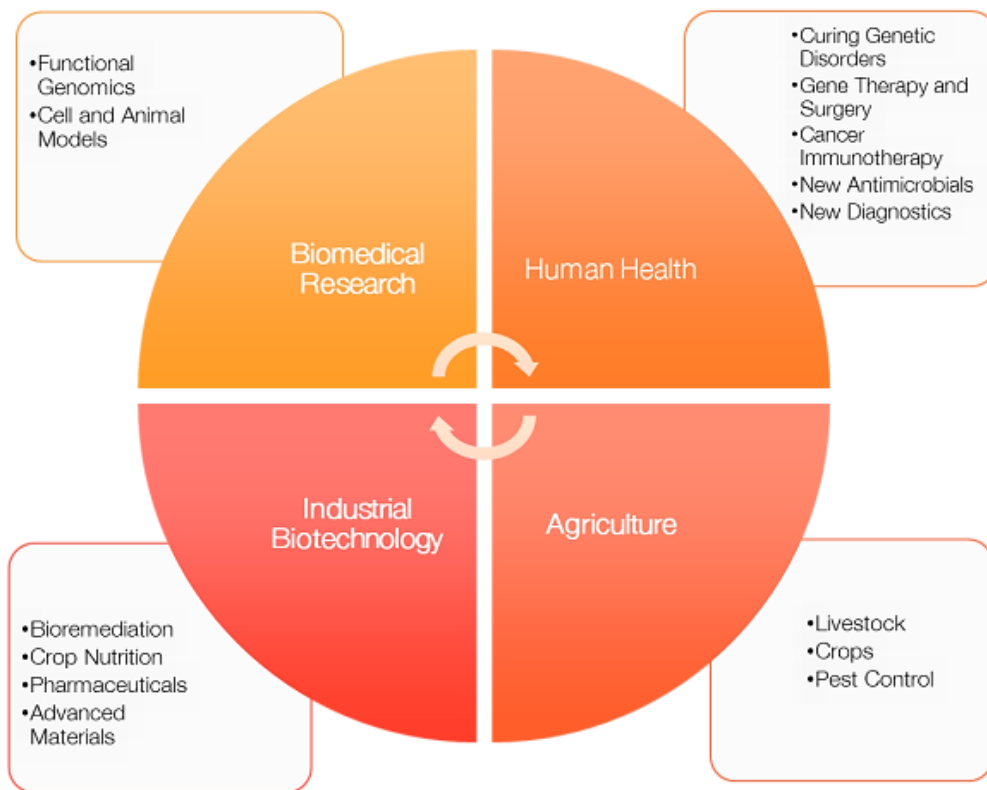


Figure C. Four broad domains of benefits and example applications facilitated by CRISPR.

Available indicators point to a rapid acceleration of technological capability, economic investment, and product development in genome editing that will have significant economic impact. The market for genome editing is expected to exceed \$3.5 billion by 2019, but a security incident, biosafety lapse, or significant regulatory uncertainty could hamper this growth.

Risks

The growth of the attack surface has expanded dramatically due the open source nature of the life sciences research enterprise, the globalization of its innovators and users, and the increasing integration of biotechnology into the economy. In addition, developments in genome editing have created new potential attack vectors and the means for rapidly identifying novel ones. Indeed, many of these new attack vectors do not involve actual pathogens, but instead relate to genetic constructs and associated means of delivery. Since the current biodefense paradigm is oriented around developing defenses against a short list of pathogens and most defenses are agent-specific, these new attack vectors have the potential to circumvent current defenses. These new attack vectors also raise new attribution challenges. Since 2001, the United States has invested heavily in microbial forensics, but again, these capabilities are geared towards the analysis and characterization of traditional bioterror pathogens. Genome editing, and CRISPR in particular, pose a new set of challenges to biosafety, biodefense, and biosecurity, thereby altering the security landscape. The landscape of risks can be viewed as comprised of four security domains, illustrated in figure D.

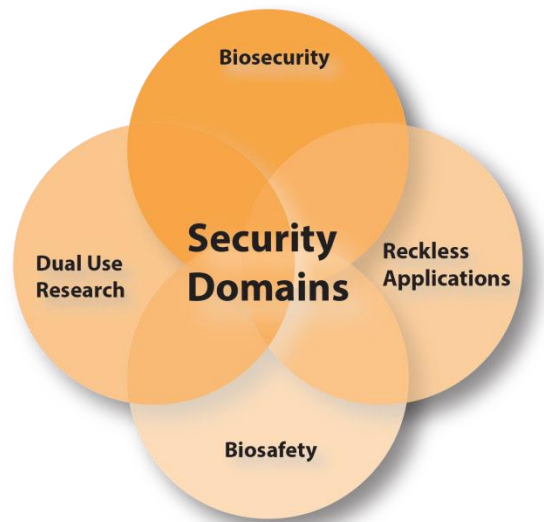
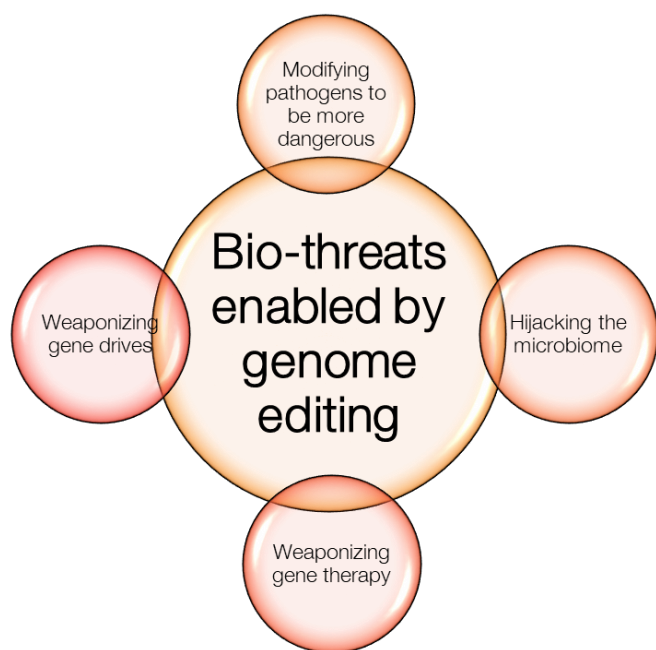


Figure D. Security domains and the landscape of risks.

Scientific, technical, economic, and social trends are increasing the range of potential biological hazards, diversifying the sources of these hazards, multiplying the routes of exposure, expanding the populations that may be exposed, and increasing these populations' level of susceptibility. The rapid diffusion of versatile genome editing tools to a broad range of users has increased the attack surface that must be defended against deliberate, accidental, or reckless misuse of genome editing technology.

CRISPR has all the hallmarks of a generative technology.

Generative technologies are versatile platforms that can be reprogrammed by developers with a range of motivations, objectives, and skills to accomplish a variety of tasks. The open source nature of the technology encourages experimentation, the development of a wide range of applications, their adoption by a diverse user-developer base, and the formation of knowledge-sharing networks and cultures which feeds further innovation. Understanding CRISPR as a generative technology helps shed light on why this technique has come to dominate the field of genome editing, the technology's implications for biosecurity, and the challenges that policy-makers face in formulating and implementing governance measures that promote innovation and reduce risks.



We identify four examples of biological threats enabled by genome editing that populate the risk landscape.

Figure E. Examples of biological threats enabled by genome editing.

Despite the potential risks, there remain significant barriers to misuse of genome editing in the near-term for states, in the medium-term for skilled groups, and in the longer-term for skilled individuals.

Scenarios, Takeaways, and Governance Options

The full report illustrates governance gaps and options across four categories. Provided within each of these categories are scenarios that were developed by drawing upon the study’s workshops, input from subject matter experts, and supplemental research and analysis. The scenarios have been grouped across these four main categories, but elements of each could appear in other categories. The scenarios are structured around concrete, yet hypothetical, examples. Mindful of potential information hazards, they have been written to be plausible, but not capable of directly enabling misuse.

Advances in genome editing have illuminated the need to examine the current state of biotechnology governance, identify gaps and areas for improvement, and provide new governance options, while ensuring the appropriate balance between promoting safety, security, and innovation.

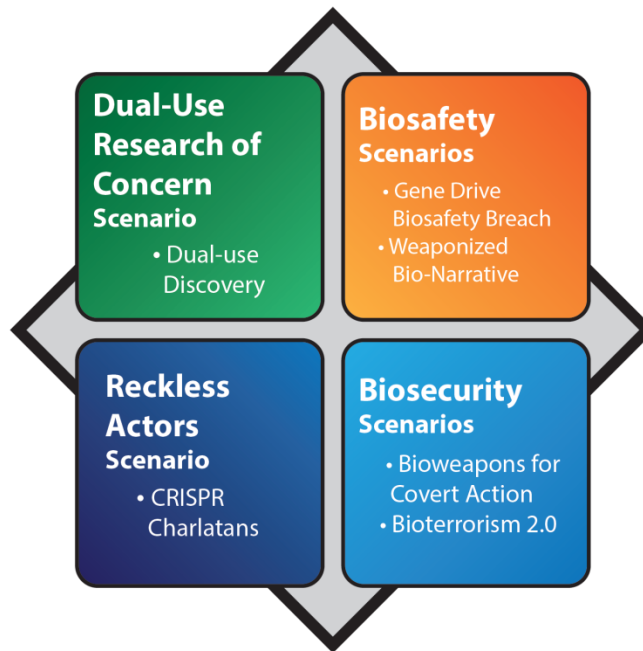


Figure F. Areas of security concern and corresponding scenarios.

The scenarios illustrate the complexity of vulnerabilities and risks, gaps in current policy and practice, and the ecosystem of actors that must be involved to manage the changing security landscape. The scenarios do not represent a comprehensive list of concerns, nor are they necessarily the most important, and they are not intended to be predictive. Instead, they are tools for illustrating gaps between current biosecurity policies and the challenges that emerging genome editing capabilities may pose in the near future.

Each scenario is coupled with examples of policy options that illustrate a range of representative approaches that could address these identified governance gaps. The options presented outline a set of approaches that could be taken to help fill some of the gaps; the approaches are not wholly conclusive, nor do they preclude other options for governance or actors who could implement such options. Finally, the scenarios offer background and context that is intended to display how the discussion and debate around genome editing, and CRISPR in particular, illuminates broader strategic, technological, and policy changes that are shaping the security landscape.

Abridged Example Scenario

Scenario Description: Bioterrorism 2.0

The scenario illuminates biodefense vulnerabilities that can emerge from an increasingly complex global ecosystem of materials and service providers for biotechnology research. It involves a terrorist group that takes advantages of commercially available resources and a lack of customer screening to use genome editing to convert a non-pathogenic bacteria into a biological weapon.

The New Dawn is a white supremacist and millenarian group dedicated to purifying society of “undesirable” elements. Instead of engaging in random acts of violence or symbolic acts of terrorism, New Dawn is pursuing an alternative method to achieving their goal of a white ethno-state. The leaders of New Dawn prey on talented, lonely individuals, particularly PhD students and post-doctoral researchers, whose social and professional achievements have not lived up to their expectations and who hold strong grievances against minority groups or society in general.

The group decides to combine their members’ limited expertise with CRISPR, and an easily acquired non-pathogenic bacteria, to create a new biological weapon. The group orders what they need to set up a rudimentary but functional lab from a variety of domestic and overseas suppliers. The backbone of their biological weapon is the innocuous *E. coli* bacteria, which can be found in the environment and the gut of humans and animals. *E. coli*’s hardiness, versatility, and ease of handling have made it a favorite microbial model organism for biologists and a workhorse for the biotech and pharmaceutical industries. These same properties also make the bacteria well-suited for the purposes of New Dawn. At first, the group tries to use CRISPR to modify a lab strain of *E. coli* to produce botulinum toxin, the most lethal toxin known to humans. One of the group’s members is able to obtain a synthetic copy of the gene coding for the toxin from a DNA synthesis firm in Asia that does not conduct sequence or customer screening. Nonetheless, this effort is unsuccessful due to the difficulty of engineering a new metabolic pathway for the bacteria to produce the toxin.

The group’s next attempt to develop a biological weapon is to engineer a different strain of *E. coli*, called O157:H7. While most strains of *E. coli* are harmless, a few can produce toxins. Due to their low infectious dose and their ability to spread through contaminated food and water, these strains can cause outbreaks of food poisoning. *E. coli* O157:H7 is one the more dangerous strains of the bacteria since it produces the shiga toxin, which can cause severe food poisoning with a lethality rate of 5-10%. The group hopes to engineer O157:H7’s existing metabolic pathway with the help of bacterial protein expression kits purchased online to increase the amount of shiga toxin produced by the bacteria. The group plans on disseminating its super-toxin producing bacteria, which should induce high fatality rates in those who consume contaminated food and beverages, in restaurants and grocery stores in predominantly minority neighborhoods.

Takeaways

- **Increasingly Complex Global Industry:** There is an increasing number and diversity of providers of materials and services supporting biotechnology research.
- **Inconsistent Oversight Standards:** Customer and order oversight and screening standards exist in some cases, but these do not cover the full global market. Other suppliers in the industry, such as genome editing software or reagent suppliers, or companies that provide on-demand biological engineering services, often lack any screening standards.
- **Experiments Evading Oversight:** Using genome editing to modify non-pathogenic bacteria to be more dangerous can circumvent oversight under the Federal Select Agent Program because the bacteria do not appear on the select agents list.

Options for Improving Oversight of Biotechnology Goods and Services

- **Industry Oversight Standards:** The U.S. government could work with providers of biotechnology goods and services to establish voluntary guidelines that include “know your customer” standards, especially for items that pose a higher risk of misuse, and systems for advice and reporting. The U.S. government could also encourage the genome editing industry to adopt a standard to use only goods and services provided by companies that adhere to customer screening standards.
- **Funding Incentives for Industry Oversight:** The U.S. could require recipients of government funding for life sciences research to purchase from companies that demonstrate a specified level of customer and order screening. Private funding bodies could, as a condition of funding, also require similar standards for researchers to purchase screened DNA.
- **Industry and International Engagement:** The U.S. government could work with other countries with large biotechnology industries, such as China, to co-develop standards, possibly via support for an international standards consortium.
- **Incentives for Research Organizations:** Journals and professional societies could only publish, or accept for presentation, research that has met screening standards.
- **Applied Security Research:** The U.S. government could continue and expand sponsored research on methods to increase the effectiveness and reduce the cost of screening. One option for DNA synthesis screening is to develop a curated database of “sequences of concern.” Another is to explore a sequence screening upgrade that utilizes one-way encryption to screen sequence fragments through an international network of cloud-based servers.

Context and Background: Synthetic DNA Screening

The International Gene Synthesis Consortium (IGSC) is comprised of leading DNA synthesis firms who voluntarily screen customers and their ordered sequences.

Synthetic DNA Screening

The field of synthetic biology is characterized by a mix of governance measures. In 2009, a group of leading DNA synthesis firms formed the International Gene Synthesis Consortium and announced that they were voluntarily adopting customer and sequence screening standards. The IGSC is comprised of 12 DNA providers, and it collectively accounts for 80% of the global market in DNA synthesis. As part of the screening process, orders are compared against a database of nationally and internationally regulated pathogens and toxins to determine if any ordered sequence poses a security risk. If the automated screening system detects a close match between an ordered sequence and a regulated agent, the order and the customer are scrutinized manually. Based on this manual analysis, the order can be filled, the company can contact the customer for more information, the order can be cancelled, or the company can contact government authorities. As the cost of DNA synthesis continues to decrease, and screening costs remain relatively stable at present, manual screening will constitute an increasingly heavy burden on the members of IGSC.

Members of the IGSC share information on a regular basis within the confines imposed by the need to safeguard proprietary business information. Implementation of the IGSC's standards, however, are at the discretion of each company, and there is no mechanism for the consortium or its members to assess the degree to which members are complying with the consortium's standards.

A gap in the standards that IGSC has yet to address is the potential for non-pathogenic coding DNA sequences, which are not covered by current screening methods, to be synthesized and used nefariously. For instance, genes relating to ecosystem niche habitat preference for a harmless organism could be ordered from a DNA provider. Using CRISPR, the genes could then be inserted into an esoteric pest species to modify or expand its range. This could result in potentially serious economic or ecological effects. This gap is especially important in the context of target selection for gene drives.

In parallel with the industry's development of codes of conduct, the U.S. Department of Health and Human Services (HHS) crafted voluntary guidelines for U.S.-based DNA synthesis providers that were published in 2010. These guidelines detail customer screening measures, standards for sequence screening, and the process for raising concerns with the appropriate government authorities. HHS recommendations only cover double-stranded DNA longer than 200 base pairs; they do not cover short oligonucleotides (single-string DNA). In addition, there is no mechanism for assessing whether companies, based in the United States or elsewhere, follow the HHS guidance.

Conclusion

The genome editing field is near an inflection point. While still a relatively new field in the annals of science, it has been six years since the publication of the seminal paper that first identified the potential of CRISPR-Cas9 to make precise edits to DNA. Because CRISPR has proven to be so versatile, it has unlocked a much broader array of capabilities that enable a wider range of actors to modify a diverse array of organisms in a multitude of ways.

Designing effective safety and security governance measures for a generative technology such as genome editing is challenging. The accessibility of the technology, in terms of acquiring the necessary material and skills to use it, makes it attractive to a wide range of actors with diverse motives and objectives. The versatility of the technology enables these actors to develop a variety of products in a number of disparate fields. The current system for governing the safety and security dimensions of biotechnology is fragmented and based on a patchwork of laws, regulations, policies, and voluntary measures at the national and international levels.

Many of the issues identified here are representative of broader systemic challenges created by advances in the life sciences and biotechnology—challenges that will grow only more complex over the long-term. Unless the process of modernizing existing governance measures to ensure the safe, secure, and responsible use of biology begins today, the scientific and policy communities will find it even more difficult to take effective action in the future.

At a minimum, existing governance measures need to be updated to consider the growing capabilities offered by genome editing in the fields of agriculture, biomedical research, human health, and the bioeconomy. In some cases, these updates will be minor and incremental. In other cases, governance measures may have to be radically revised in order to achieve the objectives for which they were designed. There may also be cases where brand-new initiatives at the national or international level are needed to fill a critical gap in the governance architecture. The path forward will require a pragmatic compromise

INTRODUCTION

In 2012 scientists discovered that an obscure bacterial defense mechanism called Clustered Regularly Interspaced Short Palindromic Repeats (**CRISPR**) could be used more widely to make precise cuts in DNA. Less than a year later, CRISPR was used to edit mammalian cells. In combination, these two developments launched a revolution in the field of genome editing that has transformed the entire life sciences research enterprise.

While the capability to modify the genomes of living organisms, known as **genome editing**, is over four decades old, CRISPR, as it is commonly referred, is the most significant recent advance and most publicly visible example of predictive genome editing technology. CRISPR allows scientists to add, delete, or modify multiple genes simultaneously with a high degree of precision. Genome editing is poised to make major contributions to basic research, medicine, public health, agriculture, and the biomanufacturing industry, thereby reducing widespread suffering and improving the human condition. This potential was epitomized by *Science* magazine's naming CRISPR as the Science Breakthrough of the Year in 2015.¹

While genome editing will enable significant beneficial contributions, there are risks associated with intentional, reckless, or accidental misuse.² Genome editing enables new discoveries about how microbes, humans, animals, and plants work, and provides new tools for manipulating these biological processes. As a result, in addition to future threats from edited pathogens, the threat landscape may be expanded to include new means of disrupting or manipulating biological systems and processes in humans, plants, and animals. The number of potential vectors, targets, and effects will grow rapidly as genome editing is used to explore and exploit biology. Genome editing could be used to create new types of biological weapons, such as those able to target the microbiome, and the immune and nervous systems. Further, the "democratization of biotechnology" may dramatically increase the number and type of individuals and groups capable of using, and misusing, genome editing. In effect, the versatility, ease, flexibility, and precision offered by new genome editing techniques, such as CRISPR, increases the **attack surface**.

Attack surface, a term originating from cybersecurity, describes the number, accessibility, and severity of vulnerabilities that could be exploited to cause harm, either deliberately or accidentally. The more ways there are to penetrate and disrupt a system, the larger the attack surface, and therefore the more vulnerable a system is to being manipulated.

Motivated by concerns such as these, intelligence agencies and militaries around the world have voiced concern about the potential risks posed by genome editing, as have numerous national academies of science.³

STUDY APPROACH

This study's purpose was to highlight the changing safety and security landscape engendered by the emergence of new genome editing technologies, help policy-makers and other stakeholders navigate this space, and illuminate broader trends in the life sciences that may impact the security landscape.

This study focused primarily, but not exclusively, on the risks associated with the deliberate misuse of genome editing technologies, with an emphasis on genome editing in **eukaryotes**, especially mammals. These risks could be the result of malicious misuse of the technology by a terrorist group, non-state actor, or government. In addition, risks may result from an accidental release of a modified organism or pathogen, unanticipated consequences of a laboratory or field experiment, or reckless behavior on the part of an actor. Measures to prevent, prepare for, and respond to risks of deliberate, accidental, inadvertent, and reckless misuse are collectively referred to as **biosecurity**. Determining the overall risk posed by genome editing technologies was beyond the study's scope.

These risks, in combination with the rapid adoption of CRISPR, motivated the four lead authors to initiate this two-year study to explore critical biosecurity issues related to CRISPR and related genome editing technologies. The overarching goal of this study was to present policy options and recommendations designed to balance the often-competing demands of promoting and protecting safety, security, and innovation. We investigated how to adapt current or create new governance mechanisms to achieve these objectives. These options range from hard law, such as legislation and regulation, to soft law, such as voluntary guidelines and safeguards built into the design of infrastructure and technology platforms, to informal measures, such as codes of conduct. These options are designed to be pursued by different sets of stakeholders.

The study leads were assisted by a core research group of fourteen subject-matter experts and seven research assistants. The centerpiece of the study was three invitation-only workshops that brought together the core research group for structured discussions of the benefits, risks, and governance options for genome editing. The study leads and research assistants prepared two working papers to frame the workshop discussions. The first working paper reviewed past studies that assessed the risks posed by emerging dual-use technologies. The goal of this working paper was to provide a baseline for understanding the security implications of genome editing and to identify best practices in risk assessment.⁴ The second working paper provided an overview of the current governance landscape for biotechnology and a framework for evaluating governance measures.⁵ Each of the three workshops included a range of scientific, policy, ethics, and security experts. We gathered additional information from our subject-matter experts in the form of five commissioned issue briefs. Several of the study's experts served as discussants who critically reviewed the content of the issue briefs through iterative commentary and feedback. All of these working papers and issue briefs are available at the project's website: <https://editingbiosecurity.org/>.

This study contributes to the existing body of studies related to a variety of security, ethical, and social issues associated with genome editing. The National Academies of Science, Engineering, and Medicine (NASEM) has examined the ethical, social, and legal implications of genome editing in humans.⁶ The ecological risks associated with **gene drives** have been examined at great length in another NASEM report.⁷ The first public risk assessment that addressed CRISPR and other genome editing technologies from the security perspective was a study undertaken by NASEM as part of a broader assessment of synthetic biology and biosecurity.⁸ This report focused on threats to U.S. civilian and military personnel. The JASON federal advisory group and biosecurity consulting firm Gryphon Scientific have also each produced reports, but these remain classified or restricted. This study was designed to engage and complement these other efforts through its emphasis on the governance issues raised by the security implications of genome editing.

The study leads and core research group have backgrounds in diverse disciplines, including the life sciences, social sciences, and the humanities, which ensured a rigorous research process underpinned by the inclusion of a variety of perspectives, and further complemented by numerous areas of expertise. It is our hope that the design of this study, including the interdisciplinary composition of the study leads and core research group, can serve as a model for future studies that seek to engage a diverse array of experts and stakeholders. In addition, the study and its products relied on unclassified, open, and publically accessible information. This study is an independent academic work in which the charge and scope were determined solely by the research team. In combination, these factors were motivated by the team's goal of producing open and accessible research outputs that can assist stakeholders in crafting better, smarter, and more informed policies.

Organization of the Report

This report is divided into six sections. Section 2 provides a technical overview of genome editing, with an emphasis on the tools, capabilities, and limitations of the technology. This overview is followed by section 3, which offers a snapshot of the potential benefits of genome editing in the domains of human health, agriculture, and the broader bioeconomy. Section 4 provides an analysis of the potential safety and security risks posed by genome editing. The section begins by outlining the landscape of genome editing risks, and then offers an overview of the general categories of biological threats enabled by genome editing. The section concludes with a discussion of the barriers to misuse of genome editing. Section 5 provides six potential security scenarios across several domains. Because the research team relied on open source, unclassified material, this report is not a comprehensive risk-benefit assessment. Rather, this report provides a suite of scenarios that illustrate a plausible range of ways in which the security-relevant characteristics of genome editing could arise in different contexts. The scenarios were not chosen to be a comprehensive list of concerns, or necessarily the most important, but illustrate the complexity of vulnerabilities and risks, gaps in current policy and practice, and the ecosystem of actors that must be involved to manage the changing security landscape. Each scenario is coupled with examples of policy options that could address these identified governance gaps. The report's final section concludes with some observations about how the discussion and debate around genome editing, and CRISPR in particular, illuminates broader strategic, technological, and policy changes that are shaping the security landscape and environment.

GENOME EDITING: TOOLS, CAPABILITIES, APPLICATIONS, & LIMITATIONS

Genome editing has emerged as a lively discipline of genetic engineering, making use of successive generations of simple and flexible tools that allow modern molecular biologists to perform an almost unlimited range of alterations to the genomic DNA in an organism's cells.

One can view genome editing from four perspectives:

- Genome editing **tools** are the specific molecular methods that are used to alter an organism's DNA. They may be used in conjunction with other tools, and as part of larger processes. The most well-known of these tools is called CRISPR.
- Genome editing **capabilities** refer to the molecular alterations and outcomes that these tools allow scientists to achieve.
- Genome editing **processes** are the technologies and procedures, not limited to the genome editing tools themselves, that are essential for planning, executing, and measuring the outcome of a genome editing activity.
- The genome editing **field** comprises the entire set of activities, technologies, cultural norms, economics, and ecosystem of developers and users associated with these techniques.

Box 1. Four perspectives from which to view genome editing.

Genome editing tools are typically composed of three components: the payload, the guidance module, and the delivery system. The most basic payload is a **nuclease** protein that can cut DNA or RNA, effectively removing or crippling a specific gene in an organism. Additional protein, DNA, or RNA can be added to the payload to insert new DNA or modulate the expression of a specific gene. Short strands of DNA or RNA, called **oligonucleotides**, can be designed using **bioinformatic** techniques to determine how to precisely edit the "target" sequence in a gene or other important genetic element. The payload is guided to its target by either a customized **binding domain** or by guide RNAs, programmable elements that act as a targeting molecule. Bioinformatic tools are typically used to predict the optimal sequence of nucleotides to construct the binding domain or to express the specific guide RNAs to enable delivery of the payload to a target. Finally, these components are assembled and delivered into cells using a genome editing vector (**GEV**).

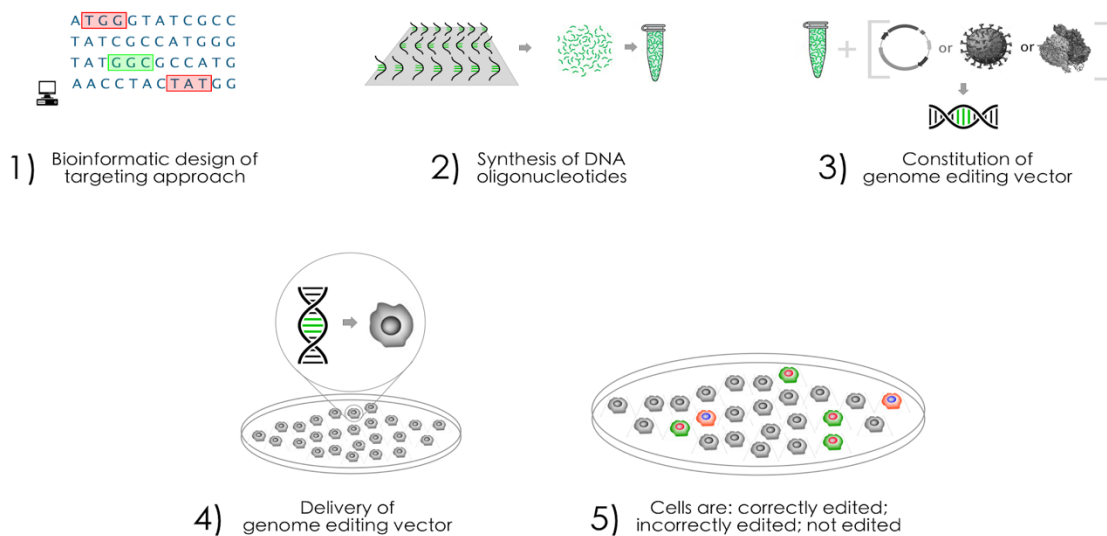


Figure A. Schematic showing basic events occurring in a standardized genome editing process: 1) bioinformatic design with selection of targets and deliberate avoidance of off-targets; 2) synthesis and manufacturing of novel programmable oligonucleotides that correspond to bioinformatic design; 3) constitution of a genome editing vector, which pairs the programmable oligo with a DNA plasmid, virus or protein, each one carrying a specific set of instructions for the cell to edit its own genomic DNA; 4) delivery of genome editing vector into cells in culture; 5) some cells in culture successfully edit their genomes on-target, others edit their genomes at off-target sites, and others remain unedited. Source: Figure A in Perello E. *CRISPR Genome Editing: A Technical and Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Genome Editing Tools

There are three primary tools used for genome editing: **Zinc Finger Nucleases (ZFNs)**, **Transcription Activator Like Effector Nucleases (TALENs)** and **Clustered Regularly Interspaced Palindromic Repeat (CRISPR)-Cas systems**. CRISPR systems are the newest and by far the most widely used of these tools. Please refer to the primer on genome editing technology by Edward Perello for more details on the history and technical characteristics of these tools.⁹

Zinc Finger Nucleases

Zinc-finger nucleases, introduced in 1996, make use of a pair of effector molecules, each with a separate DNA binding domain attached to a nuclease domain. Binding domains are built from arrays of proteins called zinc fingers that can be chained together in order to target complex genome sequences. A pair of Fok1 nuclease proteins are used to introduce a **double strand break (DSB)** in the targeted DNA. Designing and constructing effective ZFNs is a long, complicated process that requires specialized skills in protein engineering. These genome editing tools, however, have a high degree of specificity and accuracy, meaning they are less likely to have unwanted effects in other parts of the genome, known as **off-target effects**.

Transcription activator-like effector nucleases

Transcription activator-like effector nucleases were introduced in 2009. Like ZFNs, they make use of a paired doublet of two-part protein complexes and are typically delivered as plasmids, also requiring weeks or months to assemble as experiment-ready molecules. TALENs may be considered a step change as compared with ZFNs, as their construction is more straightforward and their binding activity is more predictable. Like ZFNs, TALENs has a relatively low rate of off-target effects.

Clustered Regularly Interspaced Palindromic Repeat (CRISPR)

The introduction of CRISPR as a genome engineering technique occurred between 2012 and 2013. CRISPR-Cas9 was the first in a rapidly expanding suite of **RNA-guided endonuclease (RGEN)** tools, although CRISPR-Cas12 and CRISPR-Cas14 have been added since and operate in a generally similar fashion to CRISPR-Cas9. The core of the CRISPR RGEN (see Figure B) is a nuclease called a *CRISPR-associated* or *Cas* protein, with multiple functions, one of which is to bind to nucleic acids (double-stranded DNA, in the case of Cas9), unwind it, and introduce a break at a target site. Guide RNAs, which bind to the Cas proteins and provide targeting specificity, are simple to manipulate, and act as a programmable element; they can easily be expressed as part of a single CRISPR plasmid GEV template in a process known as **molecular cloning**. While ZFN and TALEN plasmid GEVs are also cloned, the operation to assemble and test multiple plasmids to identify appropriate binding and cutting can take many months. With CRISPR, the assembly operation can be as short as a few hours to days, requiring a one-plasmid cloning operation to load a single short custom element into a standardized plasmid backbone, with a high degree of confidence that the single construct will work. CRISPR can also be delivered via numerous types of GEVs beyond plasmids, including messenger RNA, viruses, and synthetic ribonucleoprotein (RNP). The major drawback associated with CRISPR is its lower level of specificity resulting in a higher likelihood of off-target effects compared to ZFNs and TALENs, although this depends on the specific combination of editors and targets.

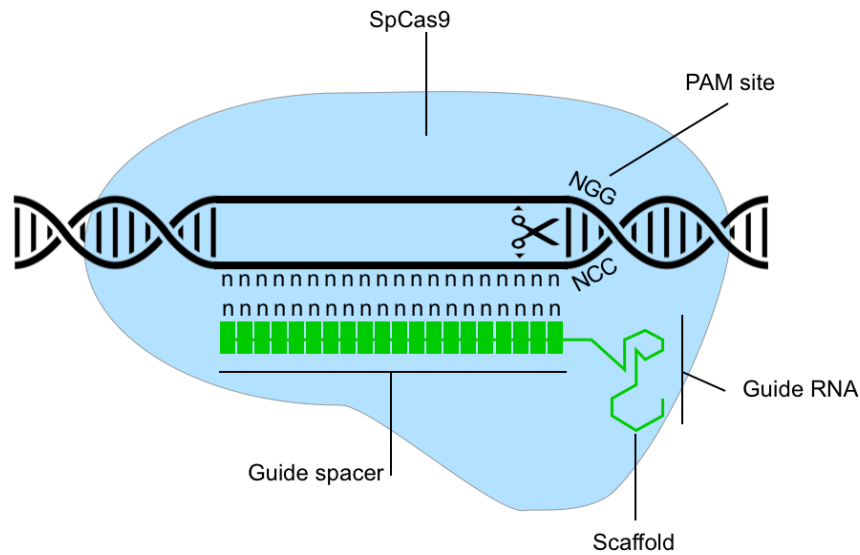


Figure B. Schematic of SpCas9 nuclease-guide-genomic DNA complex. The Cas9 nuclease unwinds double-stranded genomic DNA at a PAM site with NGG sequence and cuts at the site where guide RNA spacer matches one strand of the DNA. Source: Figure E in Perello E. *CRISPR Genome Editing: A Technical Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Figure C summarizes the primary differences between these gene editing tools in terms of the range of genome sequences they can target, the efficiency of the editing that occurs, the accuracy with which specific genome sequences can be targeted without creating off-target effects, the ease with which the optimal payload can be predicted and computationally designed to account for off-targets, and the ease of constructing a particular gene editing tool for a given experiment.

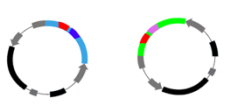

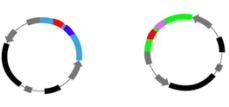
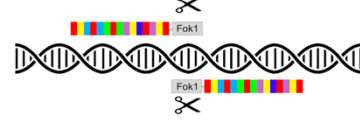

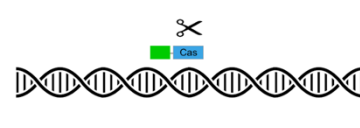
Delivery Complexity	Targeting Schematic	Summary
A) Zinc Finger Nuclease 		Targeting - almost unlimited Specificity - high Predictive challenge - high Accuracy - high Engineering - very hard
B) TAL Effector Nuclease 		Targeting - some limitations Specificity - high Predictive challenge - medium Accuracy - high Engineering - hard
C) CRISPR nuclease 		Targeting - some limitations Specificity - medium Predictive challenge - easy Accuracy - high Engineering - very easy

Figure C. Comparison of three different gene editing tools. A) Classical Zinc Finger configuration, showing doublet FokI nucleases overlapping at a target site, each attached to a unique multi-part binding domain. B) The same for TALEN configuration. C) Classical CRISPR-Cas9 configuration, showing a single Cas9 enzyme attached to a single guide RNA. Notice the relative simplicity of the CRISPR GEV format versus Zinc Finger and TALEN libraries. Source: Figure D in Perello E. *CRISPR Genome Editing: A Technical and Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Genome Editing Capabilities

This section provides a brief overview of the types of activities that are enabled by genome editing. Special emphasis is given to CRISPR since it is the most widely used genome editing tool. Three broad families of genome editing capabilities are enabled by CRISPR: cell engineering, organism engineering, and screening. Laboratories around the world are using CRISPR to support basic and translational research in academic, commercial, and biomedical settings. Cell and organism engineering have a variety of applications in these domains. The products of these engineering applications tend to have a direct value, whereas screening tends to be used primarily in a discovery setting, generating knowledge that can be exploited by additional experiments and processes.

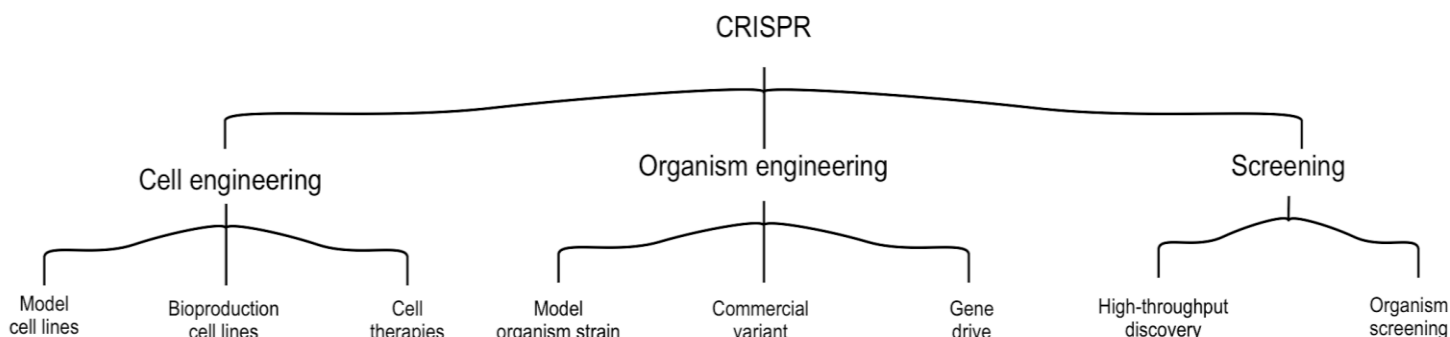


Figure D. A schematic of the basic taxonomy of CRISPR genome editing capabilities: cell engineering, organism engineering, and screening. Source: Figure I in Perello E. *CRISPR Genome Editing: A Technical Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Cell Engineering

Cell engineering is principally concerned with the deliberate and rational development of cells with specific properties derived from particular mutations. Genome editing is used to introduce mutations of interest, which enables the development of “cell lines” with stable **genotypes** over successive generations. Cell engineering supports the exploration and discovery of traits in basic and applied research, and is especially useful for deeply probing the functional relationships between a mutation and a trait. Cell lines may also be developed as advanced bioproduction platforms, in which their metabolic pathways are altered to increase production of a metabolite that is useful as an industrial feedstock or pharmaceutical compound, or to insert a novel production pathway for a new compound. Cell engineering can also be used for therapeutic purposes. Gene therapy targets diseases or conditions caused by genetic disorders by correcting the mutation(s) that cause the disease. Cell therapy creates “living drugs” by modifying intact, living cells and then injecting them into a patient. For example, the CAR-T immunotherapy cancer treatment uses genome editing to modify T cells to target specific antigens on cancer cells, which enhances the effectiveness of the patient’s immune system to identify and eliminate the cancer. Notably, these types of therapies focus exclusively on somatic cells that are not involved in the reproduction of the organism, such that “corrected genes” cannot be passed from a patient to their children.

Organism Engineering

A key objective of whole organism engineering is to develop edited organisms that reproduce amongst themselves to produce a stable lineage of offspring with those same qualities. Germline cells (such as sperm, eggs, and embryos) are exposed to CRISPR payloads, which give rise to a whole organism at the end of a conventional reproduction process. Variants of **in vitro fertilization (IVF)** may be required for different animals. In plants, where whole organisms can be clonally derived from somatic cells, these cells may be edited, and are still able to give rise to a stable adult cloned organism.

Whole edited organisms have value in research and are commonly used as models for basic and translational research. Once genotype-phenotype relationships are established in cells (considerably cheaper and easier than whole organism engineering), researchers might develop an animal model to determine if the results are conserved in the whole organism. This is particularly useful in understanding the potential non-obvious effects that editing one biological system may have on another system's performance. To this end, organism engineering is valuable for proving and disproving scientific hypotheses about gene function. Organism engineering also has high value in creating new animal strains that are engineered to have disease genotypes more similar to those found in humans, allowing higher fidelity testing and evaluation of new drugs and vaccines. Crop and animal species can also be modified to have particular fitness traits improved, productive yield increased, or nutritional value enhanced.

The use of gene editing to modify human germline cells is controversial for social, ethical, and religious reasons. A handful of experiments in China, the United States, and the United Kingdom have used CRISPR to edit human embryos for research purposes. The desirability and feasibility of editing human germlines for therapeutic or other purposes is outside the scope of this paper. These issues are being addressed in a series of international meetings organized by the leading scientific organizations in China, the United States, and United Kingdom.¹⁰

A unique type of organism engineering enabled by CRISPR are **gene drives**. CRISPR enables scientists to construct a gene drive system that can replace the original version of a gene with an edited version along with a copy of the gRNA and CRISPR protein needed to make the edit. If used in mosquitos, for example, when an edited mosquito mates with a wild mosquito, the offspring will inherit the gene drive embedded in the wild mosquito's chromosome, which will then edit the offspring's DNA (see Figure E). What makes CRISPR-based gene drives so powerful is that they can spread genes across successive generations of descendants, even if the genes do not necessarily confer a fitness advantage, potentially reshaping the genetic makeup of an entire species. The versatility of CRISPR will eventually allow scientists to build gene drive systems capable of driving through a population almost any trait that they know how to alter. Gene drive systems have so far been constructed and proven to work in yeast, flies, and mosquitoes. Notably, the first study demonstrating the capability in the laboratory showed that a second gene drive can reliably overwrite an earlier one, undoing the phenotypic change.

Gene drive technology is broadly restricted to species that exclusively reproduce sexually, that have a short generation time of roughly two years or less, and in which delivery of DNA into the germline is feasible. It is possible that additional molecular barriers that evolved to block natural gene drive systems may limit efficacy in certain species. Moreover, the difficulty of germline delivery is the primary barrier limiting accessibility in most species. Other challenges include the emergence of drive-resistant **alleles** in the targeted species and designing drives that are localized, although solutions have been proposed for solving both of these issues.¹¹ Predicting the impact of gene drives on the ecosystem that the targeted species lives in is another challenge.

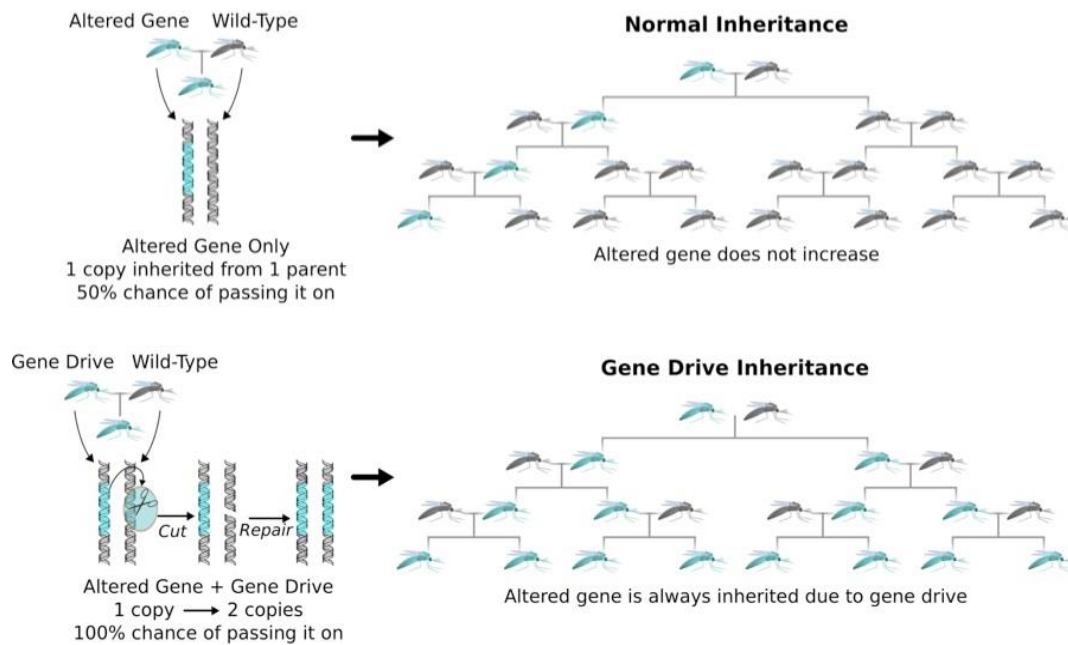


Figure E. *Normal Inheritance Versus Gene Inheritance*. Source: Wyss Institute at Harvard University.

Gene drives have potential applications in the fields of conservation, public health, and agriculture. Gene drives have been proposed for use as conservation tools to protect native ecosystems by eliminating invasive alien species, as a public health intervention by eliminating disease-carrying insects or the ability of such insects to transmit diseases to humans, and as a method of improving agriculture by eliminating harmful pest species.

Screening

High-throughput screening (HTS) capabilities make use of CRISPR in conjunction with heavily automated liquid handling platforms, measurement devices, and cell culture capabilities to conduct many millions of experiments simultaneously. Screening experiments often modify large populations of cells to discover complex multigenic phenotypes for later exploitation.

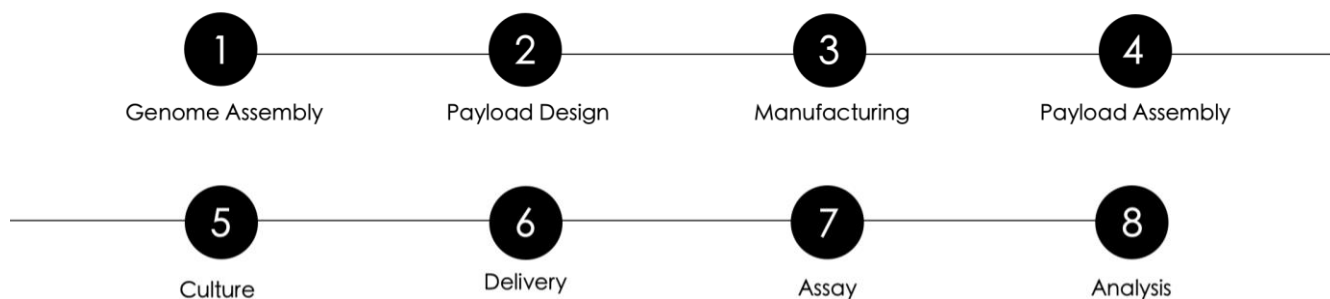
Cells are typically modified and then exposed to a selective pressure (a drug or an environmental condition) that causes edited cells to survive or die at higher rates than unedited cells. DNA sequencing identifies how particular mutant populations die off or expand in size as these stimuli are applied. HTS is highly specialized and expensive, and is typically out of reach for basic or mid-sized laboratory facilities. The activity of discovery is of great importance in the commercial biotechnology, pharmaceutical, and agricultural sectors, which can marshal the resources to execute all aspects of this process. While the advent of CRISPR has certainly reduced the biological limitations of this process by making larger libraries easier and cheaper to assemble, the operational requirement to invest in the automated facility still puts large-scale screening approaches out of reach of many.

Other CRISPR Applications

CRISPR is increasingly being used beyond the scope of *editing* and applied to other interesting problems in biology, such as biosensing and diagnostics, or to re-engineered patterns of gene expression. CRISPR approaches have been used to obtain single molecule detection. CRISPR is well-suited for diagnostic and detection applications since its components are suitable for freeze-drying and rehydration without sacrificing activity which obviates the need to rely on cold chains for storage and shipment.¹²

CRISPR Processes

Genome editing with CRISPR is not simply about the act of cutting and repairing the target DNA, but the events leading up to, and beyond, those moments, including designing the programmable elements and measuring the outcome of the work. Genome editing is thus not a discrete activity, but rather a generalizable process, with many steps and possible combinations of steps, all depending



on the specific application and desired outcome.

Figure F. An idealized CRISPR process with each step representing a distinct component of a typical genome editing experiment. Source: Figure M in Perello E. *CRISPR Genome Editing: A Technical and Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

A complete end-to-end execution of this process requires a wide range of skills. More involved genome editing applications, such as screening, when undertaken in a commercial setting will have far more complex processes, with potentially many more steps that are challenging to complete successfully. Equally, a more routine genome editing procedure, for instance a simple knockout of a gene in a well-studied organism, might have a correspondingly simpler process, with fewer steps.

The technology required to conduct genome editing with CRISPR is embodied across this process in many forms that extend beyond nucleases, guides, and genome editing vectors, and include the software, hardware, and commercially available kits and services that exist to facilitate these steps.

Depending on project complexity, either an individual or a team will take on one or more of steps, each requiring some specialist training and access to one form of CRISPR-relevant technology or another to successfully complete the procedure. While each step can be completed to varying degrees of accuracy (and some can be skipped entirely), each step will require a distinct range of laboratory tools and techniques, requiring the user to be comfortable using molecular tools and delivery techniques, maintaining viable cells or organisms over extended timeframes, and using various assays, bioinformatic design tools or analysis packages. Some steps can also be contracted out to a commercial provider. It is noteworthy that not all CRISPR users will care to execute each step to the same degree of accuracy, and this may be due to a deficit of the required skills, facilities, or funds, or otherwise simply due to a user's decision to deem one or more steps unnecessary for their particular use case. In other words, a user can execute the cleanest and most complete CRISPR genome editing process by fulfilling each step to the highest possible standard, or could settle for a quick and dirty approach that is good enough to work, but might not stand up to the rigors of academic peer review or regulatory approval.

The connection of steps within the entire genome editing process is not always a simple affair. Equipment and reagent manufacturers and other technology developers tend to create solutions for a particular step, or adjacent steps, rather than the entire process. As a result, a user may encounter problems with data transfer and biological compatibility that will need to be troubleshooted. For instance, data may need to be converted from one form to another, interpreted by distinct specialists, or outsourced to an external service provider for reformatting or analysis. Investigators may need to develop their own protocols to transfer samples between manufacturer protocols, and in many cases a protocol or kit may only be suitable for a specified organism.

A good deal of complexity is encountered when attempting to describe each of the possible routes that one could take to obtain necessary components to perform a CRISPR experiment, as not only are there many dimensions to this problem, but also many service providers and kit producers who offer CRISPR products in different forms that bridge these steps, or otherwise make them irrelevant from the user's perspective.

Obstacles and Challenges

Despite the impressive accomplishments already achieved with CRISPR, and its tremendous potential, the adoption of CRISPR has not been universal. Indeed, genome editing as a field faces important obstacles and challenges that will need to be overcome in order for the full potential of this technology to be realized across the array of applications currently under development.

Prediction of Editing

Prediction of targeting helps biologists to identify the programmable custom binding domains that are most likely to yield the desired outcome. Predictive design requires the availability of bioinformatic tools trained on a dataset of historical genome editing outcomes (i.e., biological phenotypes) for a tool in a particular context. In addition, accurate prediction of a proposed editing activity depends on having a digital representation of a target gene and a reference genome of an organism, or better yet, the actual genome sequence of an organism. While genome editing can still be achieved without some (or all) of these resources, editing procedures become increasingly complicated and error-prone as these resources are removed.

Off-target Challenges

Computational tools or scoring algorithms can be used to predict both desirable editing outcomes, and also flag the risk of potential off-target (undesirable) editing events where a binding element guides a nuclease to cut at an unintended target site. Inadvertently introduced off-target edits can disrupt normal physiological function of a cell's genes or metabolic pathways, degrading or debilitating its ability to survive and function in certain conditions. These off-target effects can have serious implications for experimental accuracy in the lab and clinically significant side-effects if they were to occur in a medical application of genome editing. Thus, minimizing off-target editing is a key requirement for unlocking and leveraging CRISPR's full potential.

Quantifying and Validating Editing

To validate conclusions and provide confidence in findings, it is important to quantify genome editing efficiency at target and off-target locations. The most salient challenge for detecting and quantifying genome editing events is in the identification of extremely low-frequency off-target events that go unpredicted, likely lying beyond the scope of training data or the resolution of high coverage sequencing instrumentation if the target genome is a complex one.

Multiple Alleles and Mosaicism

Organisms can have more than one copy (allele) of a gene, and while the sequence of this gene can be targeted, not all copies may be identical at the start, and not all copies may be successfully targeted and modified in the same way. This can give rise to mosaic cell populations or whole organisms (when they are multicellular), in which different cells have different numbers of alleles disrupted, potentially leading to different rates of gene expression. Germline mosaicism produces organisms with a mutant copy of the gene in only some of their cells and tissues, and somatic mosaicism results in only the cells closest to the injection site being edited. The severity of the problem caused by the production of cells or organisms with multiple variants depends on the context and objective of the project. For instance, mosaic cell therapies used in patients would be intolerable for almost every clinical intervention as each cell could perform differently, but mosaics in animal editing could be less problematic.

Somatic and Germline Editing

There is a stark difference between the requirements of germline and somatic editing. Germline editing is typically more difficult to achieve as it requires an operator to have highly sensitive reproductive biotechnology capabilities, whereas somatic cells can typically be obtained and handled more easily in bulk culture using simpler cell biology capabilities. To avoid germline mosaicism, it is necessary to deliver genome editing payloads to organisms before or shortly after fertilization, which can be especially challenging.

Delivery

Perhaps the most important barrier that genome editing needs to overcome is the safe and efficient delivery of genome editing molecules to the correct cell, tissue, or organ. A variety of techniques have been developed for delivering gene editors to cells in a test tube (*in vitro*), to cells and tissues in a living organism (*in vivo*), and cells and tissues removed from a living organism (*ex vivo*). Viral vectors have been the primary means of delivering gene editors in humans. More work, however, needs to be done to enhance these vector systems by improving production methods, efficiency, specificity, payload capacity, and safety. Non-viral vectors and physical methods for delivering genome editing constructs into cells have also been developed.¹³

The Rise of CRISPR

CRISPR is one of many genome editing tools that collectively comprise the emerging biotechnology enterprise. In fact, genome editing has been well-supported by an environment with 50 years of historic innovation in biotechnology, and a healthy market that both supplies and demands new genome editing tools and capabilities in an increasingly commoditized manner.

Why has genome editing, and CRISPR in particular, caused such a stir?

Early genetic engineering technology and tools were cumbersome to use and difficult to direct. Integration of new genetic material often occurred at random sites throughout a genome, potentially disrupting other mission-critical sequences, with successful modifications occurring at a considerably low frequency among cultured cells. Consequently, the majority of early genetic engineering projects instead relied on inserting DNA into organisms at non-genomic sites such that this additional DNA could function outside the context of genomic DNA. This function remained so long as the introduced DNA was able to avoid degradation or expulsion by the cell. For the most part, this extrachromosomal DNA approach was only practical in bacteria and other microbes, and while there was much success in microbial genetic engineering, progress in mammalian (and therefore human) cells was slow - as it was with many other non-bacterial organisms. A specific, directable, and scalable way to introduce permanent edits to any cell in any organism would be a significant milestone in genetic engineering.

CRISPR has emerged as the dominant genome editing tool due to a combination of technical and non-technical factors.¹⁴ In the lab, CRISPR offers the molecular biologist a number of biological advantages over existing technologies in terms of accessibility, scalability, economics and infrastructure. Other advantages include the simplicity of design and construction, the ease of use and control of CRISPR systems, flexibility of use cases, and wide support across a range of organisms.

As a result of these features, CRISPR has made it easy for researchers to edit genomes with lower investments of capital, pre-experiment labor, and time costs, in a broader range of organisms than older generations of genome editing tools permitted. By shifting a significant portion of the genome editing process from an expensive multi-step protein engineering project with significant room for error and repeated optimization, to a one-step cloning project, the biological and laboratory barriers to genome editing were lowered. These factors alone provided a step-change in capability, elevating CRISPR to the position of genome editing tool of choice.

These purely technical factors, however, do not explain the rapid uptake of CRISPR and displacement of other genome editing tools. The legal and organizational ecosystem that has evolved around CRISPR, including a permissive intellectual property environment for researchers, is also a part of this story. Despite the intense patent fight between the Broad Institute and UC Berkeley, CRISPR technology has been made available to the research and non-profit communities, which greatly facilitated access to it. In addition, non-exclusive licensing by the Broad Institute to companies wishing to sell CRISPR tools, reagents, and services for basic and translational research helped create a thriving marketplace. The non-profit Addgene's distribution infrastructure has also played an important role in the rapid, global diffusion of CRISPR to labs of all sizes. Addgene has helped scientists take advantage of this permissive intellectual property environment by serving as a repository and broker for plasmids that carry the instructions necessary for CRISPR and CRISPR-expression elements to be booted up in a cell. By enabling scientists to acquire the latest CRISPR

plasmids quickly and cheaply (\$65 per plasmid, at the time of this writing), Addgene accelerated the distribution of the technology and the know-how needed for its adoption.¹⁵ As a result, Addgene has emerged as the most-used source for labs to acquire the capabilities to use CRISPR in their research.¹⁶ Since 2013, Addgene has shipped over 100,000 CRISPR plasmids to more than 75 countries worldwide.¹⁷ These factors were instrumental in ensuring that the early-adopter interest was met with sufficient supply, guaranteeing wide and rapid uptake of this technology.

Between June 2012, the date of the first paper describing the use of CRISPR as a genome editing tool and the end of 2017, there have been 8,074 CRISPR papers - an average of 125 papers per month – published by more than 54,133 authors and co-authors.¹⁸

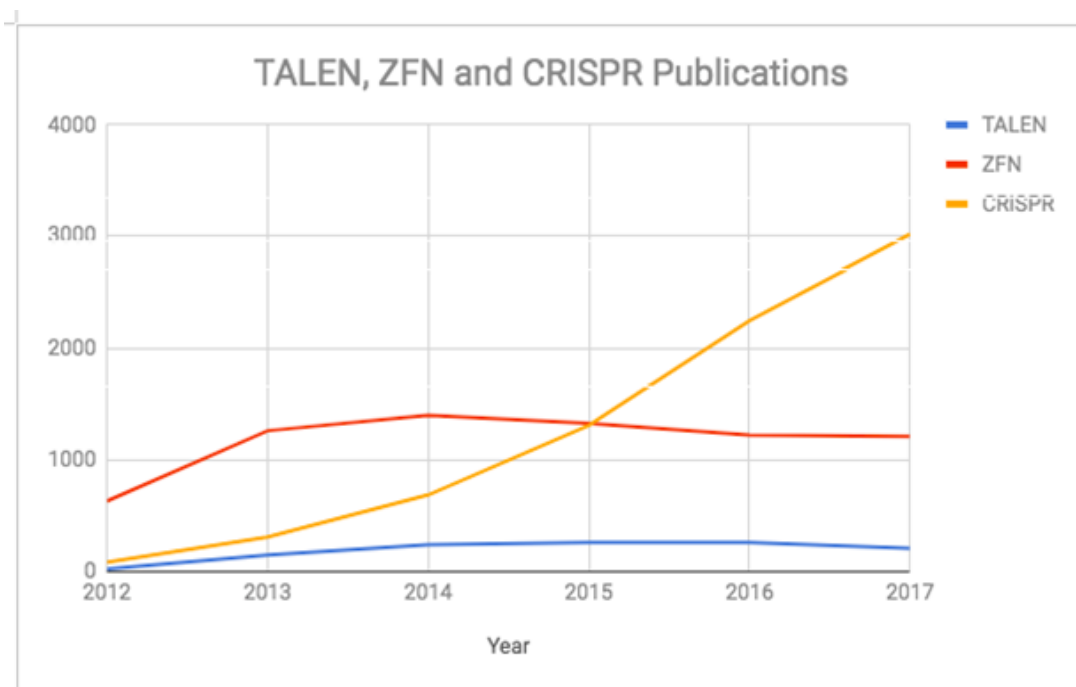


Figure G. *Scientific Papers Published on ZFN, TALENs and CRISPR, Between 2012 and 2017.* Source: Figure F in Perello E. *CRISPR Genome Editing: A Technical Policy Primer.* Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Scientific, legal, and organizational factors have contributed to making CRISPR the dominant genome editing tool of choice. This dominance of CRISPR in the gene editing field can be described as a virtuous cycle.

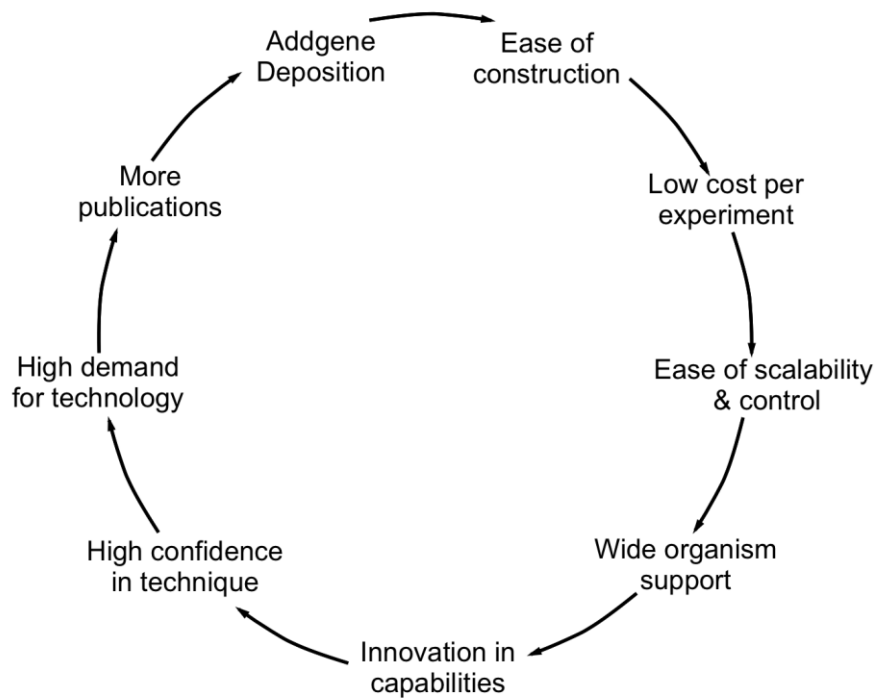


Figure H. Schematic of the virtuous cycle underpinning the evolution and rapid adoption of CRISPR technology among life scientists. Source: Figure H in Perello E. *CRISPR Genome Editing: A Technical and Policy Primer*. Editing Biosecurity Issue Brief No. 1. Arlington, VA: George Mason University; December 2018. Available from: www.editingbiosecurity.org.

Together, these scientific, legal, and organizational factors have combined to promote high rates of publication of CRISPR papers, stoking further interest by prospective and existing users. Throughout the scientific and general media, the explosive CRISPR uptake has been referred to as a “CRISPR craze,” but such notions fail to recognize the self-sustaining and positive feedback dynamics of this phenomenon. The dominance of CRISPR in the gene editing field is perhaps better described as a virtuous cycle (see Figure H) and has shown little sign of abating as the tool cements itself into the routines of biotechnology laboratories around the world. Consequently, CRISPR has emerged as the *de facto* genome editing tool of choice.

CRISPR as a Generative Technology

CRISPR has all of the hallmarks of a **generative technology**. Generativity refers to a “a system’s capacity to produce unanticipated change through unfiltered contributions from broad and varied audiences.”¹⁹ Generative technologies are versatile platforms that can be reprogrammed by developers with a range of motivations, objectives, and skills to accomplish a variety of tasks. The open source nature of the technology encourages experimentation, the development of a wide range of applications, their adoption by a diverse user-developer base, and the formation of knowledge-sharing networks and cultures, which feeds further innovation. Understanding why CRISPR is a generative technology helps shed light on this technology’s implications for biosecurity and the challenges that policy-makers face in formulating and implementing governance measures.

The rise of CRISPR demonstrates how the technology embodies the five mutually reinforcing features of generative technologies: leverage, adaptability, accessibility, ease of mastery, and transferability.²⁰

Leverage is a measure of how effective a technology is at performing a specific task or set of tasks. CRISPR is a high-leverage technology that enables scientists to modify genomes at a much lower cost, on a larger scale, and with more precision and reliability than previous genetic engineering technologies.

Adaptability refers to how easily the system can be modified to broaden the range of tasks it is able to perform, especially those not considered or intended by the original inventor. CRISPR has evolved into a versatile platform technology capable of performing many functions in a range of microbial, mammalian, and plant species. In addition to its original use to make permanent changes to DNA sequences in a genome, CRISPR can also be used to activate or inhibit the expression of genes on a temporary basis, edit RNA, perform live-cell imaging of DNA and RNA, and detect nucleic acids for diagnostic purposes.²¹ The analogy of a Swiss Army knife is frequently invoked to illustrate the adaptability of CRISPR (see Figure I).

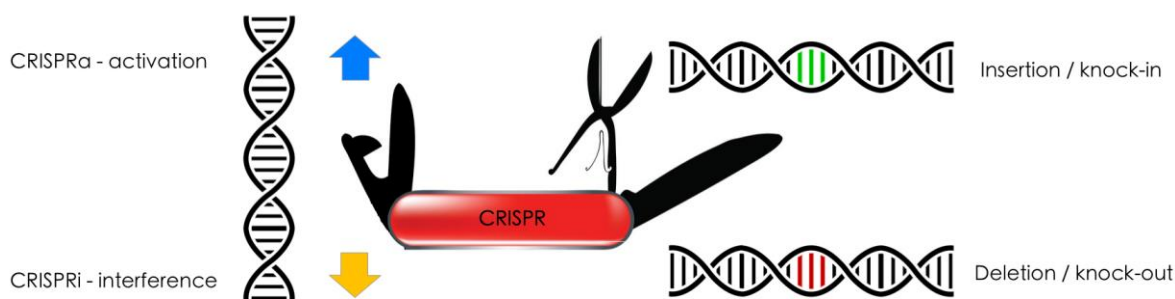


Figure I. *CRISPR as the Swiss Army knife of biology.*

Accessibility refers to the ease of acquiring the technology as well as the tools and information needed to master it. Due to the permissive approach to intellectual property and the distribution system pioneered by Addgene, the key components to use CRISPR can be acquired easily and cheaply from a variety of sources. In addition, many of these sources provide written protocols and instructional videos on how to use the technology. The accessibility of CRISPR is demonstrated by the adoption of the technology by members of the citizen science movement and by community labs.

Ease of mastery measures how much knowledge, expertise, and time is necessary for broad audiences to understand, adopt, and adapt a technology. The more useful a technology is to both amateurs and professionals, the more generative it is. Amateurs with minimal expertise may only be able to use the technology for basic tasks, but users with higher levels of expertise can unlock a wider range of applications. One of the major advantages of CRISPR over other genome editing technologies is that a primary skill needed to utilize CRISPR is molecular cloning, a common laboratory technique, as opposed to expertise in protein engineering required by other forms of genome editing technologies, such as ZFNs and TALENs. Conducting high-quality experiments does require different types of expertise in order to use bioinformatic tools and deliver the CRISPR payload to the intended target. Nonetheless, the barrier to entry for genome editing is much lower with CRISPR than other genome editing tools.

Transferability refers to how easily modifications to the technology, its supporting tools, or the associated knowledge and expertise, can be conveyed to and utilized by other developers and users.²² Addgene has emerged as a clearinghouse of not only CRISPR plasmid and reagents, but also the know-how necessary to use the technology.²³ In addition, major commercial vendors, such as Synthego and Desktop Genetics, provide comprehensive resources. The emergence of online multimedia sites, such as the *Journal of Visualized Experiments*, a peer-reviewed scientific journal that publishes experimental methods in video format, provides new ways for scientists to share their “show how” with a global audience.²⁴

The generative nature of CRISPR helps explain how this capability came to dominate the field of genome editing, its rapid uptake by a wide array of users around the world, including citizen scientists, and ever-increasing number of applications devised for this tool. Inherent in generative technologies, however, is the potential for individuals, groups, or governments to develop destructive applications or to use applications designed for peaceful purposes in a malicious manner. The

paradox of generativity is that the characteristics that make the technology so amenable to exploration, also make it open to exploitation, increasing the risk that the technology could be misused, inadvertently or intentionally.²⁵

Since the early 2000s, a number of frameworks have been proposed for assessing the risks posed by dual-use biotechnologies.²⁶ Together, this body of research has identified a number of variables or risk factors that can be used to assess the level or degree of risk posed by a particular technology or capability. These variables correspond strongly to the characteristics that make generative technologies so distinctive such as accessibility, ease of use, and versatility.²⁷ The commonality of these variables with the properties of generative technologies illustrates why genome editing arouses such concern about its potential for misuse.

Summary

Genome editing has emerged as a lively discipline of genetic engineering, which can be viewed from four perspectives:

Genome editing *tools*

Genome editing *capabilities*

Genome editing *processes*

Genome editing *field*

CRISPR has emerged as the *de facto* genome editing tool of choice through the combination of scientific, legal, and organizational factors. These factors form a virtuous cycle, which helps explain the dominance of CRISPR in the genome editing field.

Genome editing as a field faces important obstacles and challenges that will need to be overcome in order for the full potential of this technology to be realized across the array of applications currently under development.

CRISPR has the hallmarks of a generative technology. Inherent in generative technologies is the potential for individuals, groups, or governments to develop destructive applications or to use applications designed for peaceful purposes in a malicious manner. Understanding why CRISPR is a generative technology helps shed light on this technology's implications for biosecurity and the challenges that policy-makers face in formulating and implementing governance measures.

The properties of generative technologies, combined with corresponding risk factors that can be used to assess the level or degree of risk posed by a particular technology or capability, illustrates why CRISPR arouses such concern about its potential for misuse.

BENEFITS OF GENOME EDITING: A SNAPSHOT

Genome editing, and CRISPR in particular, holds great promise for enabling major advances in a wide range of fields. Available indicators point to a rapid acceleration of technical capability, economic investment, and product development in genome editing. The market for genome editing is expected to exceed \$3.5 billion by 2019. A security incident, biosafety lapse, or regulatory uncertainty could hamper this growth. Biosecurity and economic security are interconnected.

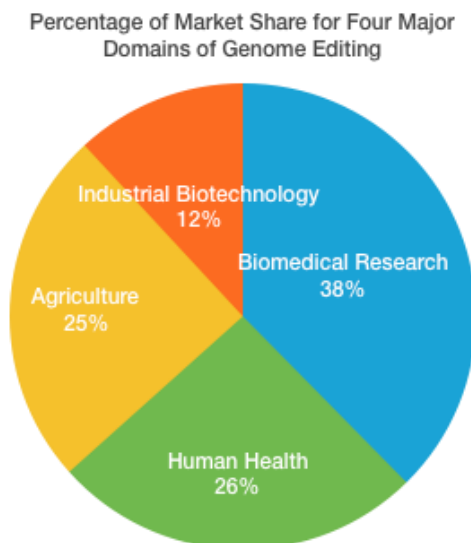


Figure J. Chart based on data in Brinegar K, Yetisen AK, Choi S, Vallillo E, et al. The commercialization of genome-editing technologies. *Critical Reviews in Biotechnology* 2017 Nov; 37(7): 924-932. DOI: 10.1080/07388551.2016.1271768.

This section describes the potential benefits that genome editing can bring in four broad domains: biomedical research, human health, agriculture, and industrial biotechnology. In a field as fast moving as genome editing, this report can only offer a snapshot of the potential benefits and some of the key obstacles to realizing those benefits.

Biomedical Research²⁸

CRISPR has the potential to make significant contributions in the area of biomedical research.

Functional Genomics: CRISPR has already shown itself to be a valuable research tool in uncovering the purpose of individual genes and the relationships between clusters of genes in a range of organisms. With CRISPR interference, a catalytically dead Cas9 (dCas9) can be used to silence the expression of individual genes. By using a library of gRNAs covering the host organism's genome, individual genes or gene clusters can be knocked down in parallel to identify which genes' silencing leads to changes in the organism's survivability and other traits. Thus, in one straightforward experiment a list of genes involved in pathogen biogenesis can be obtained and further studied for mechanistic understanding, or the gene targets could serve as potential drug targets for treatment development. Similarly, CRISPR interference knockdowns can be used to target an agent of interest to determine the function of the agent's genes without needing to make a recombinant virus, which can be time-consuming. In addition, individual gene functions can be tested quickly and easily using CRISPR without the need to create transgenic cell lines or animals.

Another major area where genome editing technologies will continue to have a major impact is the discovery and understanding of agent replication mechanisms. CRISPR screens used to identify key genes in these pathways are likely to play an increasingly important role in quickly identifying what factors of infection are important to consider when developing treatments. In terms of understanding the introduction of factors enhancing virulence, CRISPR/Cas genetic tools are likely best employed to understand the evolving host-pathogen relationship from the host perspective via gene screening, as CRISPR/Cas tools have not been used for engineering viruses, and many viral engineering tools already exist.

Cell and Animal Models: One of the biggest changes in biomedical research brought about by genome editing, and especially CRISPR, is the ability to create new cell and animal models quickly and efficiently. Unlike existing technologies such as ZFN and TALEN, CRISPR does not require redesign of the effector nuclease, only the guide RNA. Synthesizing guides are relatively inexpensive and many can be tested in a short period of time. Further, the high activity of Cas nucleases results in a higher probability of making a desired mutation or change, shortening screening times which becomes more significant as the maturation time of the model organism increases. The faster turnaround time of new model organisms benefits biological research as a whole, allowing for a more appropriate testing environment, less time spent building research materials, and more time collecting novel data. Similarly, the development of monoclonal antibodies (mAbs) and vaccines for prophylactic treatments can benefit from CRISPR/Cas9 through increased rates of cell line generation and the ability to perform genomic screens to identify what epitopes are targeted by mAbs.

Human Health

CRISPR has the potential to contribute to public health and medicine in myriad ways, including curing and treating genetic disorders, developing new cancer therapies, new antimicrobial and

antiviral drugs, diagnostics, and means of controlling disease-causing insects. Yet translating promising bench research into therapeutic drugs faces significant technical hurdles such as off-target editing, which creates the potential for permanent unwanted edits to a patient's genome, and providing safe and efficient delivery of the Cas protein and gRNA without triggering the patient's immune system. The problem of Cas protein complex packaging and delivery is likely to be one of the primary scientific challenges facing the CRISPR research community as it shifts to translational research. Significant efforts are underway to overcome these technical bottlenecks in order to eliminate or treat genetic disorders, develop cancer therapies, develop antimicrobials, and diagnostics.²⁹

Curing Genetic Disorders: The human health application for genome editing that has received the most attention is **germline editing**--the editing of human eggs and sperm (known as germ cells) and embryos-- to correct genetic disorders in utero. Genetic changes introduced into germ cells and embryos are permanent and would be inherited by future offspring. Researchers in China, the United States, and the United Kingdom have conducted human germline editing experiments on non-viable embryos.³⁰ These projects have fostered widespread debate about the ethical and social implications of such work. One of the most prominent concerns centers on the possibility that such research could enable heritable genetic changes that are designed for enhancing individuals, and not just for therapeutic purposes.³¹ International discussions are ongoing regarding the conditions under which human germline editing research is acceptable.³²

Gene Therapy/Surgery: Given the scientific uncertainties and ethical concerns associated with germline editing, near-term medical applications are focused instead on **somatic (non-heritable) genome editing** of human cells for therapeutic purposes. One class of medical applications, collectively known as gene therapy, takes advantage of the ability of genome editing tools to make small and precise changes to DNA to treat monogenetic disorders that are caused by mutations in a single gene. It is estimated that the genes responsible for half of the approximately 7,000 monogenetic disorders have already been identified.³³ Clinical trials to treat inherited blood disorders and rare metabolic disorders are underway using ZFNs and further clinical trials are planned using CRISPR-based gene therapies.³⁴

Cancer Immunotherapy: Another promising area where CRISPR-based therapies have also advanced to conducting clinical trials is cancer therapy. Clinical trials are underway in China and approved in the United States to develop *ex vivo* immunotherapies where immune cells are removed from a patient, edited in a lab to improve their effectiveness against cancer cells, and then administered back into the patient.³⁵

New Antimicrobials: CRISPR has the potential for developing novel antimicrobial and antiviral drugs for use against retroviruses, RNA viruses, and bacteria. For example, retroviruses like HIV can be removed from the population by excising the viral DNA from the host's genome, an approach which has already been tested in mice. Directly targeting viruses is also a potential route to treating disease outbreaks. CRISPR-based antivirals are particularly promising because it is comparatively easier to generate large numbers of guide RNAs relative to the difficulty of developing small molecule drugs to which pathogens will likely eventually evolve resistance. Since the World Health Organization (WHO)'s list of high-priority diseases that lack effective treatments or vaccines is dominated almost exclusively by RNA viruses, we are likely to see a significant expansion in the use of RNA targeting and editing. Additionally, concerns over off-target edits to patient genomes

increases the attractiveness of direct RNA targeting or editing. Separately, viral infections could be combated by editing the human genome to resist viral infections altogether. For example, CRISPR could be used to modify key protein receptors to mimic the rare mutation that provides innate immunity to HIV. Genome editing also has the potential to develop new ways of targeting bacteria to counter the rising tide of antimicrobial resistance.

Diagnostics: CRISPR has been used to design paper-based diagnostic systems for the detection of bacteria or viruses. These diagnostics are cheap, field deployable, and well-suited for low-resource settings where public health laboratories with sophisticated diagnostic capabilities are absent or in low supply. SHERLOCK, which uses the Cas13 protein, has demonstrated the ability to detect RNA viruses such as Zika in human samples while DETECTR, which uses the Cas12a protein, has been able to reliably detect and distinguish between two closely related strains of the DNA virus human papillomavirus (HPV). Future improvements to stimulate Cas protein activity, increase signal-to-noise strength, and shorten assay run time may make these types of paper assays a standard field method for agent detection.

Vector Control: Vector-borne diseases, such as malaria, Zika, and dengue, are major threats to global health, causing tens of millions of illnesses and at least one million deaths a year, primarily in less developed countries.³⁶ Existing control measures based on anti-malaria drugs and vaccines, bed-nets, use of insecticides, and habitat destruction to reduce vector populations have contributed to a steady decline in malaria cases, but scaling-up these measures is costly and the spread of resistance to drugs, vaccines, and insecticides threatens to undermine the progress made so far.³⁷ Gene drives could be designed to either reduce the population of disease-carrying insects and parasites (called a population suppression strategy) or alter the vector to render it unable to transmit disease (a population replacement strategy). The most advanced work in this area is focused on reducing malaria transmission by *Anopheles gambiae sensu lato* mosquitoes, the primary vector for this disease in sub-Saharan Africa.³⁸ Scientists have already developed a gene drive that can sterilize female insects with over 90% efficacy.³⁹

Agriculture

Genome editing has a range of potential commercial applications in the agricultural sector where the technology can be used to improve the nutritional value, yield, and other desirable properties of plants and animals.⁴⁰

Livestock: Animal engineering is one area where genome editing is likely to play a major role. CRISPR-based tools allow for easier editing of mammalian genomes, with most applications focusing on germline edits. Several genome editing applications, such as those that reduce susceptibility to disease, have already been demonstrated in economically important animals such as cattle and pigs. The availability and capabilities of *in vitro* fertilization facilities will likely impact which animals are considered good candidates for editing, the types of edits that will be possible, and which actors will be able to utilize genome editing on animals. Cattle breeders are increasingly adopting *in vitro* fertilization techniques with some companies now offering *in vitro* fertilization along

with embryo micromanipulation and other tools that would allow easy genome editing. *In vitro* fertilization is less common for pigs, but genome editing techniques for these animals are rapidly being developed. In addition to serving as a food source, pigs are also of interest for biomedical reasons since they are an important model system for studying a number of human diseases and as hosts for humanized organs that could be transplanted into humans. As these *in vitro* fertilization and editing capabilities become more sophisticated, widely available and easier to use, the possibilities for genome editing in other mammals, including humans, will expand.

Crops: Genome editing has also made an impact in plant engineering, including easier and more efficient editing of a wider range of plants, such as maize, rice, and soybeans. These applications have clear economic implications driving research and development, with opportunities for crop improvement through higher yields and increased drought tolerance, pest resistance, and herbicide resistance. A lack of regulatory oversight by the USDA for many genome edited plants is also pushing development of genome editing tools over traditional transgene-based products, which are subject to regulation as genetically modified organisms (GMOs).

To date, plant engineering has been dominated by large corporations, primarily in the United States, where engineered crops are grown at large scales. Genome editing tools have the potential to decrease the cost of developing engineered plants, allowing a wider range of actors to develop new products, including those tailored to crops that have been traditionally less profitable than others. 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, especially multigenic traits that depend on multiple genes. Improved knowledge of this basic biology is likely to expand the types of traits that can be engineered into crops and other plants.

There remain several technical challenges to using genome editing tools in plants, with transformation of plants a key bottleneck. CRISPR-based genome editing in plants still relies on the 30-year-old technique of using *Agrobacterium* to transfer DNA into plants, but there has been renewed interest in developing new methods for transformation. Many plants have highly repetitive DNA sequences and polyploidy (i.e. having more than two copies of each chromosome), making it difficult to ensure that a CRISPR construct has edited all targets without off-target edits. Also, many plant species repair their DNA in ways that allow CRISPR to disrupt their genes but which make the insert of new DNA more difficult. To date, only well-resourced labs have been able to accomplish knock-in of DNA sequences using CRISPR-based methods.

Pest Control: Gene drives have been proposed for use as a method of improving agriculture by eliminating harmful pest species such as certain types of insects and rodents. It is estimated that insects cause crop losses totaling more than \$400 billion a year with billions more lost to pests affecting livestock. Efforts to control such pests with chemicals has been challenging due to the negative impact of such chemicals on non-pest species and on human health, and the emergence of resistance among the targeted pest species.⁴¹ Given their short generation time, insects are a natural target for gene drives. Gene drives could be designed to suppress the population, reverse resistance to insecticides, make the organism more susceptible to a new, less toxic compound, eliminate an insect's desire for human crops, or remove other traits that allow it to survive, reproduce, or cause harms to crops and livestock.⁴² Gene drives that distort the sex ratio of vertebrate pests, such as mice and rats, have also been proposed as a means of reducing or eliminating these populations.⁴³ Research is underway to develop a gene drives for the spotted wing

Drosophila (Drosophila suzukii), a fruit fly native to Japan that is now found all over the world. The insect is a major global crop pest because it lays its eggs in ripe fruit, instead of in rotten fruit as is typical of other types of fruit flies.⁴⁴ However, current self-propagating gene drive systems are unsuitable for any of these applications, as models predict that they will invade all populations of the target organism connected by gene flow throughout the world.

Industrial Biotechnology

A growing segment of the bioeconomy is engineering bacteria and yeast to produce commercially valuable compounds such as fuels, pharmaceuticals, fragrances, advanced materials, and other high-value products.⁴⁵ Companies are developing microbes that could be directly applied in the environment for bioremediation, biomining, or crop nutrition. For many microbial applications, CRISPR-based genome editing may be helpful, but it is just one tool among many that have been developed for engineering microbes. So far, the declining cost of synthetic DNA has been the main driver of growth in this market segment, with automation and bioinformatics playing important roles as well. 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. CRISPR may also 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.

Summary

Genome editing is a powerful technology that promises a wide range of benefits across a number of domains. Realizing these benefits over the long-term will partly depend on society's ability to facilitate beneficial research and prevent, or if necessary, mitigate the potential risks posed by the technology. Despite the promise of a wide range of benefits, barriers to use remain.

Available indicators point to a rapid acceleration of technical capability, economic investment, and product development in genome editing.

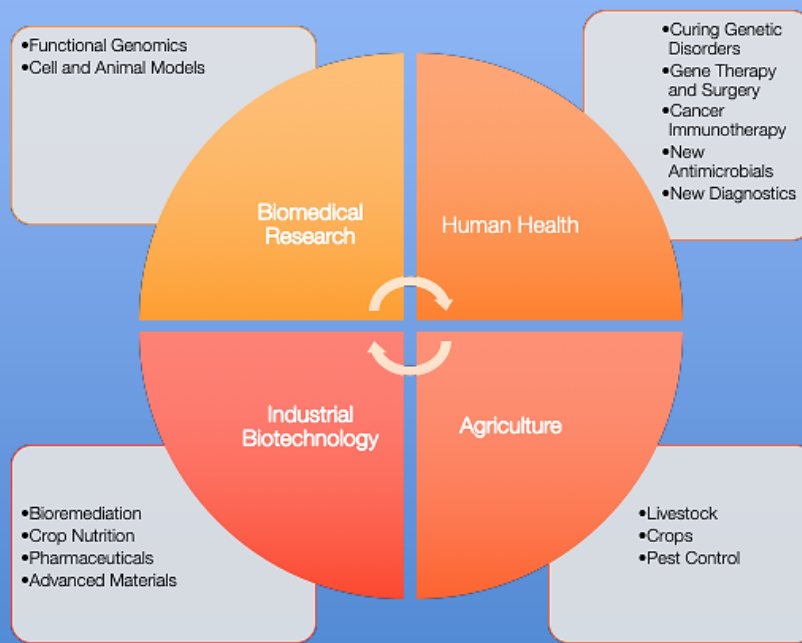


Figure K. *Four broad domains of benefits and example applications facilitated by CRISPR.*

Nevertheless, a security incident, biosafety lapse, or regulatory uncertainty could hamper this growth and the realization of benefits that could significantly improve the human condition.

SAFETY AND SECURITY RISKS ENABLED BY GENOME EDITING

As with recombinant DNA in the 1970s and the emergence of synthetic biology in the 2000s, the rise of genome editing technologies, especially CRISPR, has raised hopes and fears about its impact on science, public health, medicine, the economy, and society. Although many of the risks and rewards under discussion today are the same ones featured during previous debates about recombinant DNA and synthetic biology, there are some notable differences.

This section describes how genome editing is expanding the range of potential safety and security hazards. This section is not intended to provide an exhaustive analysis of all of the potential safety and security risks posed by genome editing. Instead, this section provides an overview of the leading concerns with regards to dual-use research, biosafety, biosecurity, and reckless applications. These potential hazards are then illustrated in section five by a series of vignettes that provide concrete, yet hypothetical, examples of how these risks could emerge given current technological trends and existing governance gaps.

Landscape of Genome Editing Risks

Scientific, technical, economic, and social trends are increasing the range of potential biological hazards, diversifying the sources of these hazards, multiplying the routes of exposure, expanding the populations that may be exposed, and increasing these populations' level of susceptibility. The rapid diffusion of versatile genome editing tools to a broad range of users has increased the attack surface that must be defended against deliberate, accidental, or inadvertent misuse of genome editing technology. The cybersecurity community uses the concept of attack surface to describe the number, accessibility, and severity of vulnerabilities in information technology systems that could be exploited to cause harm, either deliberately or accidentally. The more ways there are to penetrate and disrupt a system, the larger the attack surface, and therefore the more vulnerable a system is to being manipulated. DNA, the code of life, is increasingly vulnerable to manipulation by a diverse array of actors with a range of motivations and capabilities.

New genome editing techniques such as CRISPR can offer greater flexibility, precision, and versatility than previous approaches and provide scientists with a new suite of tools that can be used to explore and exploit a variety of potential applications. These applications include engineering cells (single-celled microbes) to have new properties, altering the genetic makeup of organisms (plants and animals, including humans) through somatic or germline editing, and spreading genetic traits through a population using gene drives. These new editing capabilities translate to both quantitative and qualitative differences in how genetic functions are targeted in a much wider array of species by more versatile engineering platforms with more diverse potential applications. Moreover, developments in associated technologies including DNA synthesis and automation combined with

these functionalities means that genetic landscapes can be explored more efficiently. At the same time, each of these application categories could be used to cause harm, whether deliberately through the creation of a biological weapon, accidentally in the event of a biosafety failure that results in the escape of an engineered organism into the environment, inadvertently through the discovery of new knowledge or vulnerabilities, or recklessly through inappropriate conduct that harms the health of humans or the ecosystem. The likelihood and consequences of each of these risk pathways depends in large part on the intent and capability of the actor involved.

The technical advantages of CRISPR, coupled with its affordability and accessibility, has led to the rapid adoption of this technology by a range of actors. The high rate of diffusion of these technologies also means that many more people are capable of exploring this landscape and exploiting what they discover. Genome editing has been adopted not only by established practitioners of molecular biology such as those working in government laboratories, large corporations, and universities, but also by non-traditional citizens or do-it-yourself (DIY) scientists working in community labs and start-ups.

The range of applications enabled by this technology in the human health, agricultural, and industrial sectors provides strong incentives for governments, companies, and research institutions to invest in improving the accuracy, efficiency, predictability, usability, and affordability of genome editing.

Globalization and the emergence of centralized repositories such as Addgene that facilitate sharing technology and know-how further reduces geographic and financial obstacles to accessing the technology.⁴⁶ Nevertheless, accessing the technology differs from translating that technology to work in the ways that the actor intends. The sophistication of the work conducted by these different actors varies greatly, but it should not be ignored that genome editing technology can be found in government labs as well as garages.

The increasing diversity in the types of actors engaged in genome editing, in terms of motivation, objective, and capability, also means that the potential sources of risk are diversifying. The vast majority of actors who work with genome editing technology do so with benevolent intentions and the goal of making positive contributions that improve scientific understanding, human health, agriculture, and the environment. Even scientists with the best of intentions, however, can pose risks in the form of dual-use research and biosafety failures. There is also a class of risks to human health and the environment that are engendered by reckless applications of genome editing technology, especially in areas that might fall outside the scope of current regulatory frameworks. Finally, there are state and non-state actors with malevolent intentions who may seek to use genome editing to engage in biological warfare or biological terrorism.

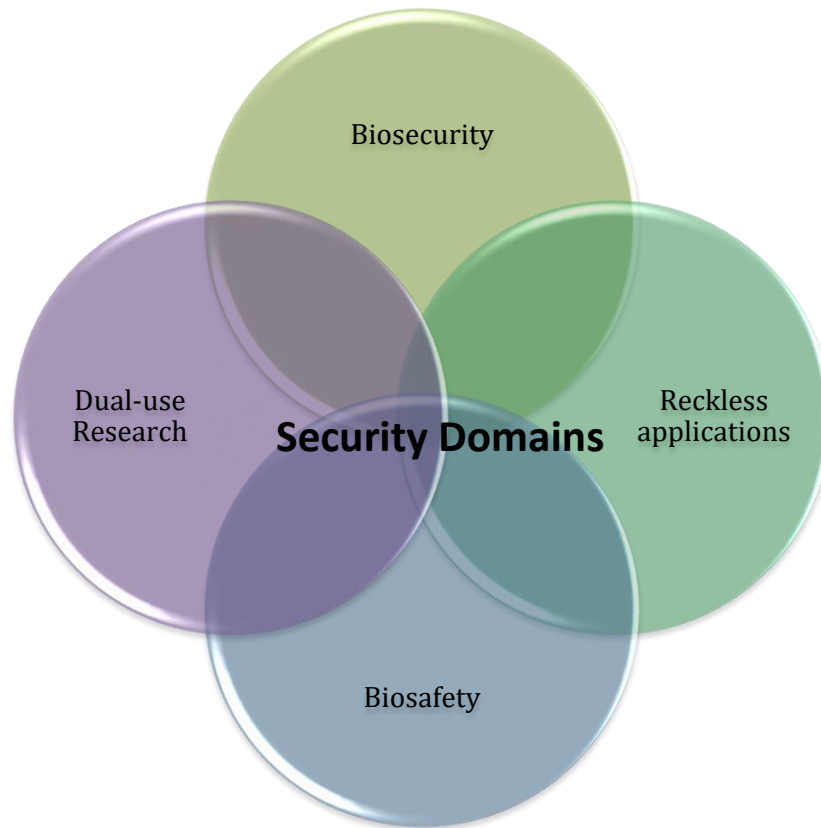


Figure L. Security domains and the landscape of risks.

Dual-Use Research

The life sciences have long been characterized by “dual-use” research that is conducted for peaceful purposes, but can generate technology, knowledge, or materials that could be misused to cause harm. Prominent examples of dual-use research controversies include the 2001 mousepox experiment that demonstrated how to engineer a pox virus to overcome vaccine-induced immunity, the 2011 “gain of function” experiment that created a strain of H5N1 avian influenza that could spread between mammals, and the 2018 synthesis and rescue of horsepox virus that demonstrated how to resurrect an extinct virus closely related to the one that causes smallpox.⁴⁷

There are already clear indications that genome editing possesses dual-use concerns. For example, researchers who sought to make pigs resistant to a devastating disease for the pork industry used CRISPR to replace a key receptor for the virus in pigs with a structurally similar, analogous human receptor. While this change succeeded in reducing the infectivity of the virus in pigs, it also created conditions that could favor the mutation of the virus to gain the ability to attach to these human-like receptors, which could enable the virus to potentially infect humans as well. In effect, in the process of reducing the threat posed by this livestock disease, the scientists inadvertently increased the risk of generating a new zoonotic disease. This risk was only recognized by one of two groups of scientists working in this area.

The development of gene drives also illustrates that dual-use research is not always recognized as such by the scientists involved. The earliest inventors recognized the potential impact that gene drives could have on animal populations in nature and on entire ecosystems. These scientists, led by Kevin Esvelt at MIT, made these concerns public and crafted a voluntary code of conduct and biosafety measures for research with gene drives before beginning laboratory experiments.⁴⁸ However, another group of scientists, who were not exposed to this work, independently developed the same technology as a tool for studying genetics in a laboratory setting without realizing the risks of its potential to spread in the wild.

A recent NASEM report repeatedly notes an important obstacle to using genome editing, including its use for malicious purposes, is the lack of knowledge about the relationship between genotype and phenotype.⁴⁹ Just as a detailed understanding of human anatomy is as important to a surgeon as a sharp knife, scientists need a deep understanding of how genetic changes result in a desired physical trait or other outcome in order to utilize genome editing technologies effectively. CRISPR not only enables scientists to better exploit current knowledge of how genes function, but high-throughput screening enables scientists to explore functional genomics at an accelerated pace and on a larger scale. Since understanding how genotype influences phenotype is a barrier to many of the malicious applications identified by the NASEM report and others, breakthroughs in understanding the functions of genes in humans, plants, and animals, is bound to create dual-use knowledge about new vulnerabilities. In addition, the use of powerful approaches based on genetic selection with the use of effective environmental conditions and a suitably large pool of genetic variants may circumvent the need for predictive knowledge about genotype-phenotype relationships.

CRISPR therefore poses a double-edged risk: it will provide capabilities for accelerating and expanding our understanding of functional genomics as well as the tools needed to exploit these discoveries, for good or for ill.

Biosafety

Biosafety is the field of work and study devoted to containing biological hazards, thereby preventing laboratory workers, the local community, and the environment from accidental exposure, and in the case of infectious pathogens, from subsequent infection. Life sciences research intended to enhance scientific understanding of infectious diseases or develop improved medical countermeasures and diagnostics poses an intrinsic risk of accidents that could lead to the infection of a laboratory worker or the escape of an organism into the environment. For example, during the summer of 2014, the Centers for Disease Control and Prevention (CDC), one of the nation's premier biomedical research organizations, suffered a string of biosafety mishaps involving *Bacillus anthracis* (the bacterium that causes anthrax) and avian influenza.⁵⁰ These accidental and inadvertent sources of risk are inherent by-products of a robust biomedical research enterprise and the field of genome editing will not be immune to them.

Genome editing poses a variety of biosafety risks. The biosafety concern that has received the most public attention, but probably poses the least risk to the public, is posed by community labs and

citizen scientists. Despite scary headlines, the vast majority of citizen scientists surveyed in 2013 reported that they worked with non-hazardous organisms that qualify for handling at the lowest level of biosafety.⁵¹ These labs also can provide a common space to learn skills as well as safety practices. Nonetheless, not all labs are equipped to provide this guidance and some people still work outside these spaces. Operating outside of established research institutions that provide training, guidance, and resources to ensure that research is conducted under the appropriate biosafety conditions, non-traditional researchers are still at risk from accidental infections and for causing environmental releases. For example, in 2017, Germany severely restricted the import of genome editing kits after finding that some of the kits sold by a U.S. company that caters to the citizen scientist market were contaminated with pathogenic bacteria, including antibiotic resistant strains.⁵²

The genome editing application that raises one of the greatest concerns from a biosafety perspective is gene drive. At present, federal biosafety guidelines have not yet been developed for gene drive research, and shipping regulations for current NIH Guidelines treat a standard self-propagating gene drive no differently than a recombinant organism.⁵³ When linked to particular functions, the accidental release of a self-propagating gene drive into a wild population could have far-reaching results.⁵⁴ In addition, one of the primary safety concerns associated with gene drives is not confined to infections at the individual level, but ecological risks at the population level, which complicates the application of traditional biosafety risk assessment methods.⁵⁵

Reckless Applications

Reckless behavior also has the potential to cause harm. The adverse effects of this behavior may not be anticipated or sufficiently well understood, or may be well-known but not adequately protected against. It is easy to imagine an actor with benevolent motives slipping into reckless conduct in an effort to accelerate the research process, boost profits, gain publicity, or otherwise put their own private interests ahead of the public good. The risk of recklessness grows in proportion to the increasing number of actors using these technologies. This is especially true when genome editing applications can be developed outside of regulatory systems that are designed to reinforce benevolence and detect and deter reckless behavior.

The emergence of an extensive network of stem cell clinics in the United States that market unapproved medical treatments should serve as a cautionary tale. According to a 2016 study, there were 570 clinics in the United States offering unapproved treatments for medical conditions and for cosmetic enhancement.⁵⁶ Dozens of similar clinics operate around the world.⁵⁷ These sites do not offer the handful of stem cell therapy treatments licensed to target blood cancer, but instead they provide unapproved therapies for a wide range of other diseases and medical conditions whose safety and efficacy is undocumented.⁵⁸ Stem cell “treatments” have resulted in a range of adverse effects ranging from blindness to death.⁵⁹

There is a risk that regulatory loopholes and lax enforcement of existing regulations could allow the widespread adoption of unapproved products created using genome editing. In addition, these poorly overseen products may also introduce other vulnerabilities that could be intentionally exploited. Not only could such products pose a risk to public health, but if the harm they cause is of

sufficient scope and/or severity, it could cause a public backlash against genome editing more broadly.

Another illustrative risk of a reckless actor is that posed by a poorly designed or rushed field trial of a gene drive. Given the lack of experience with gene drives and the complexity of ecosystems, there is a concern that gene drives released intentionally into the wild for the purposes of disease eradication, vector control, or biodiversity conservation, could unpredictably destabilize population dynamics, have an unintended impact on species not originally targeted by the gene drive, or have other ecological side effects.⁶⁰

Biosecurity

On the other end of the spectrum are actors with malevolent intent who could seek to use genome editing technology for nefarious purposes. There is no open-source evidence at this time of any state or non-state actor demonstrating malevolent intent to use genome editing to cause harm. There are, however, worrisome indications that such actors could emerge in the future.

Russia is suspected of having retained elements of the former Soviet Union's biological warfare program.⁶¹ The former Soviet BW program supplied weapons to the military for use during military conflicts and to the KGB for use in assassinations and other clandestine operations. After signing the 1972 Biological Weapons Convention, the Soviet Union launched an ambitious, but not always successful, initiative to use genetic engineering to develop new and improved biological weapons.⁶² For example, the Soviet BW program experimented with pathogens by inserting genes that coded for proteins or peptides that could disrupt the host's immunological and neurological systems.⁶³ In 2012, then-Prime Minister Vladimir Putin and Minister of Defense Anatoly Serdyukov spoke publicly about developing weapons "based on new physical principles," such as genetics.⁶⁴ Given these conditions, it is not unreasonable to be concerned that Russia, and other states, may have interests and incentives to explore the utility of genome editing for the development of new and improved biological weapons.

While a handful of terrorist groups have in the past demonstrated an interest in biological weapons, there is no open source evidence that contemporary groups such as al Qaeda and the Islamic State are investing in this type of engineering capability. Nonetheless, groups such as the Islamic State, which have evinced an apocalyptic ideology, engaged in extreme levels of violence, including the attempted genocide of the Yazidi ethnic group in Iraq, extensively utilized chemical weapons, and demonstrated a high degree of technical innovation by weaponizing commercially-available drones, represent an ongoing concern. Furthermore, the emergence of individuals and groups interested in and capable of engaging in bioterrorism has historically come as a surprise.⁶⁵ The diffusion of the technology and know-how associated with genome editing may make these tools more accessible and attractive to non-state actors that seek to cause harm for political or religious purposes, or who wish to cause fear through grabbing headlines by maliciously using a new technology.

There is also the potential for individuals or small groups that start with benevolent intentions to develop a malicious motivation due to radicalization, psychological distress, disgruntlement, or other factors. Such insider threats are a particularly worrisome source of concern since the perpetrator will already have relevant knowledge, expertise, and access to resources that an independent actor

would need to spend considerable time, energy, and money to acquire. For example, the Federal Bureau of Investigation (FBI) accused Bruce Ivins, an anthrax researcher at the U.S. Army Medical Research Institute of Infectious Disease, the military's premier biodefense research facility, of being responsible for the 2001 anthrax letter attacks.

A 2018 report by the National Academies of Sciences, Engineering and Medicine (NASEM), *Biodefense in the Age of Synthetic Biology*, provides the most comprehensive assessment of the utility of advanced biotechnologies for the development of new and improved biological weapons. The report covered a range of biotechnologies under the broad umbrella of synthetic biology, including genome editing, that could have direct impacts on human health. Threats to animals and plants, which could have indirect effects on human health, were outside of the scope of that study. The report ranked a dozen capabilities enabled by these new technologies based on the level of concern that they could be misused (see Figure M). Genome editing could be used to achieve objectives found in two groups of capabilities (marked with yellow boxes in Figure M)--modifying bacteria and viruses to be more dangerous, and manufacturing hazardous chemical and biochemicals--but there are several other methods that could be used as well. Genome editing certainly contributes to traditional concerns that pathogens could be made more dangerous by altering their virulence, transmissibility, or other relevant properties. While this possibility is worrisome and does present challenges to current biodefense capabilities that tend to be agent-specific, genome editing capabilities do not present a fundamental change in the threat landscape, due to the availability of other genetic engineering tools in general to accomplish these types of modifications.

More worrisome are new modes of harm that are either unique to genome editing or are greatly facilitated by advances in this technology. For three categories of capabilities (marked with red boxes in Figure M)--modifying the microbiome, modifying the immune system, and modifying the human genome--genome editing can make unique or significant contributions to realizing these capabilities. The potential to use gene drives to modify the human genome, which the NASEM report ranked as the lowest of concern, is not capable of having a meaningful effect on a sizable population in a reasonable amount of time given the long generation time of humans. An additional capability worthy of consideration, but excluded from the scope of the NASEM report, are gene drives that could be used to spread deleterious genes in plants and animals.

Highest Concern

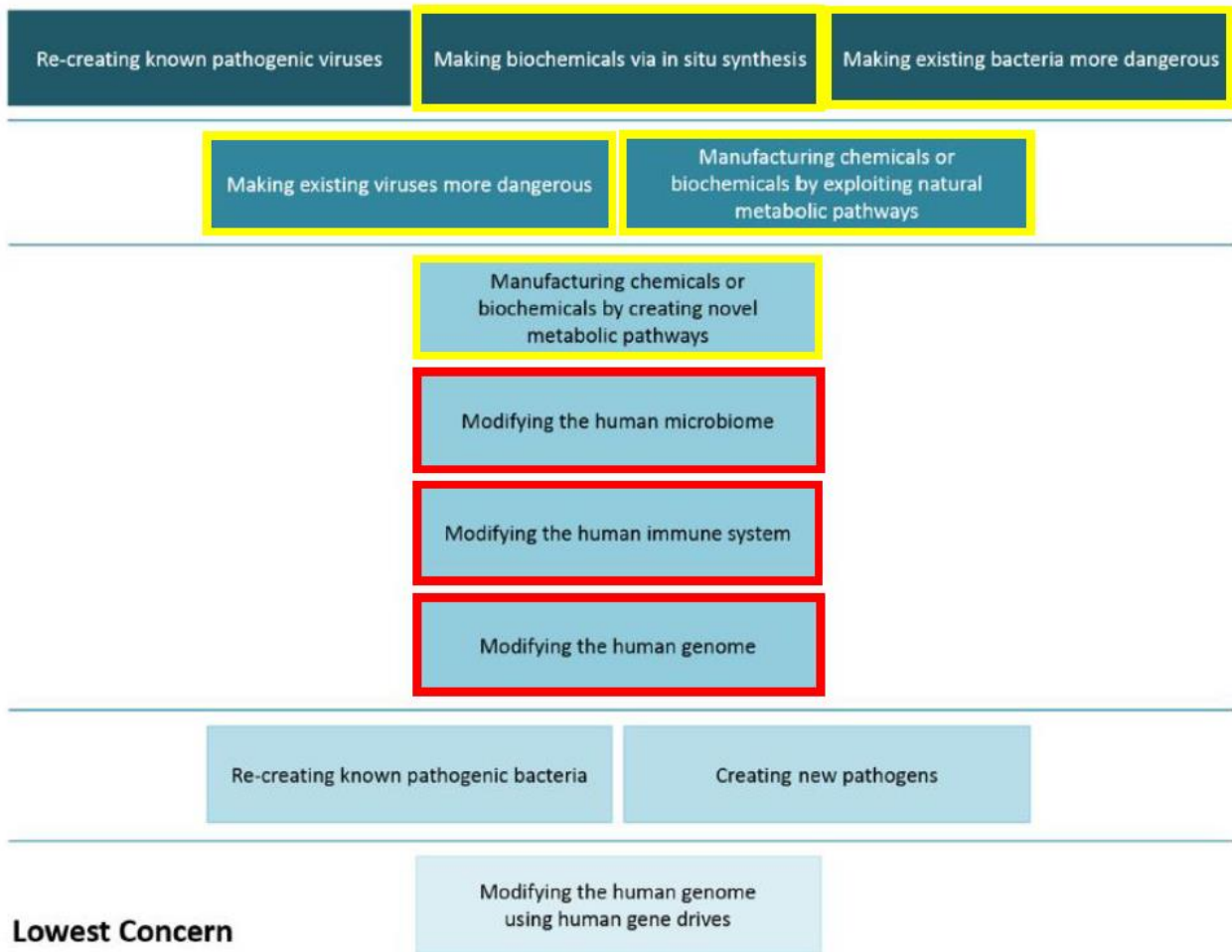


Figure M. *Level of Concern Regarding Misuse of Genome Editing*. Source: Adapted from NASEM. *Biodefense in the Age of Synthetic Biology*. Washington, DC: National Academies Press; 2018.

Note: Yellow boxes indicate capabilities that could be achieved by genome editing in addition to several other methods in molecular biology. Red boxes indicate capabilities for which genome editing has unique or significant advantages.

General Categories of Biological Threats Enabled by Genome Editing

A brief overview of four general categories of biological threats enabled by genome editing follows. These include: modifying pathogens to be more dangerous, hijacking the microbiome to produce harmful compounds, using CRISPR to modify human DNA or gene expression to cause harm, and

building gene drives that can be used to spread deleterious genes in plants and animals (see Figure N). Barriers that may slow or prevent the development of malicious applications are also included.



Figure N. *Examples of biological threats enabled by genome editing.*

Modifying Microbes to Be More Dangerous

Since the dawn of the biotechnology revolution, there have been concerns that microbes could be genetically engineered with properties that would make them more effective as biological weapons. This could entail traditional biological warfare approaches of endowing pathogens with enhanced properties such as increased infectivity, virulence, pathogenicity, transmissibility, and/or stability; resistance to medical countermeasures such as vaccines, antibiotics, or antivirals; or the ability to avoid detection and diagnosis.⁶⁶ Alternatively, a non-pathogenic organism could be engineered to produce harmful biochemical compounds such as toxins or anti-metabolites that can disrupt cellular metabolic processes.⁶⁷ Thus, there is a fairly long list of specific traits or properties that would confer an advantage in the context of biological warfare or biological terrorism.

CRISPR enables more precise and extensive genetic modifications than previous techniques, but there are a number of challenges to applying this tool to developing enhanced biological weapons with new phenotypes.

One fundamental challenge is the limited understanding of how the genotype of an organism translates into different phenotypes. In some cases, the phenotypic traits of interest (such as tropism

or transmissibility) may be the result of an interaction between multiple genes that is not well characterized. In other cases, these traits may be the product of an interaction between the pathogen and host factors and therefore not easily influenced by changing only attributes of the pathogen. In addition, given the interrelationship between different parts of a genome and different phenotypes, genetic modifications designed to affect a specific trait have some chance of influencing other traits which could reduce the fitness of the engineered organism.⁶⁸ The types of changes that would be easiest to make in bacteria and viruses would be those that increase their resistance to antibiotics and antivirals, respectively. This is because the genotypic modifications necessary to yield these phenotypes are well-characterized, and because genetic selection schemes are easy to design and execute. CRISPR has already been used to insert antibiotic resistance into bacteria.⁶⁹ Since there are already a variety of genetic engineering techniques available that enable these types of modifications to be made in many pathogens of interest, this use case does not present a novel risk.⁷⁰

Although versions of CRISPR have been developed that can edit RNA, RNA viruses lack the necessary genetic repair mechanisms that CRISPR takes advantage of for genome editing. DNA viruses are suitable targets for genome editing, but current approaches are limited by off-target effects and sub-optimal efficiency rates.⁷¹ In addition, the increasing capability to synthesize small viral genomes offers a more direct route to developing an engineered agent than using genome editing. For these reasons, the following discussion will focus on using CRISPR to edit bacterial genomes, although large DNA viruses (and some fungi) might be attractive targets as well.

Utilizing CRISPR to enhance the dangers posed by a bacterial pathogen faces significant challenges.⁷² These obstacles exist when trying to edit well-characterized bacteria that have been widely exploited for scientific and commercial applications, and are even more acute when considering more esoteric bacteria that are traditionally used for biological warfare. First, the knowledge developed to understand one microorganism does not automatically translate into the ability to effectively manipulate another organism.⁷³ Every bacterial species is unique. Second, CRISPR's efficiency across different strains of bacteria from the same species is variable. Instead of relying on an off-the-shelf annotated reference genome, researchers would likely have to try and fail several times before they could develop a workable model for bacterial genome editing that is specific to the strain they wish to alter.

Other challenges relate not to the organism itself, but to our understanding of how the organism works, how genotype affects phenotype, and how to tell if the edit is having the desired effects. These three challenges all fall under the broad category of functional genomics and highlight not only the importance of prior knowledge for applying CRISPR, but also the importance of databases and software, and expertise in bioinformatics, for successfully editing an organism. A prerequisite for CRISPR to work properly is identification of the spacer sequence (and PAM sequence, for some Cas proteins) that are used to guide CRISPR to the right point in the genome. Therefore, researchers might need to devote significant time and energy developing a standardized database of such information for the specific strain they are working on before an algorithm can be developed to identify the optimal sequence. On the other hand, the low cost of guide RNAs and the possibility of testing a large number in a relatively short period of time means that deep *a priori* knowledge is not an absolute requirement. Finally, there is no well-developed standard for evaluating CRISPR sgRNA design for bacteria and archaea, which complicates the design process and the use of CRISPR for even conventional knockout and knock-in applications for these organisms.

For scientists and companies, there are strong incentives to solve these challenges for organisms that have research and commercial utility. Annotated databases exist for genomes of nearly all major bacterial pathogens. However, for less well-known organisms there may be more need for up-front investment. This might place the capability to edit a traditional biological warfare agent to be more virulent or transmissible or otherwise dangerous outside of the reach of terrorists or criminals who lack sufficient funding and expertise. Nevertheless, the better studied the organism is, the lower the barrier.

State-run biological weapons programs are likely to have the foundational knowledge about pathogen genomics and the resources to edit these pathogens using CRISPR. It is also possible that CRISPR may provide a means for such programs to achieve objectives for which traditional genetic engineering approaches have failed. For example, during the Cold War, the Soviet Union attempted to develop a strain of multi-drug resistant *Francisella tularensis* (the agent of tularemia) for their biological weapons program. But attempts to develop such a strain failed because the drug-resistant strains lost their virulence.⁷⁴ CRISPR holds the potential to allow a modern-day bioweaponeer to take steps toward overcoming this technical hurdle. At the same time, the off-target effects observed with CRISPR may mean that bioweaponeers would face the same challenge with unwanted phenotypic changes as seen with the use of earlier genetic engineering techniques.⁷⁵

An alternative approach for a less well-endowed actor would be to leverage the high and growing level of knowledge about non-pathogenic organisms of scientific and commercial value to develop a biological weapon. This pathway may be particularly attractive for a malicious non-state actor given the relative difficulty of accessing dangerous pathogens due to the biosecurity regulations that restrict access to laboratory stocks of such agents in many countries. While natural outbreaks of highly pathogenic microbes occur regularly around the world, there is no public evidence that a terrorist group has successfully acquired a virulent pathogen from nature. The expanding number of applications of CRISPR to a variety of non-pathogenic organisms of scientific and commercial interest means that the knowledge and expertise to modify such agents is increasing. Nonetheless, in nearly all cases, converting a non-pathogenic organism to one that is pathogenic on its own for most humans, is difficult at best and nearly impossible in most cases, without re-designing the organism in a comprehensive fashion.

Hijacking the Human Microbiome

Genome editing could be used to hijack the human **microbiome** to cause harm. The human microbiome consists of trillions of microorganisms that live symbiotically with their human hosts, primarily in the gut.⁷⁶ Knowledge about the role and importance of the microbiome for human, animal, and ecosystem health has grown tremendously thanks to initiatives sponsored by NIH, the European Union, and other research funding organizations. The goal of the initial \$150 million NIH Human Microbiome Project was to characterize the microbial communities found at several different sites on the human body and to analyze the role of these microbes in human health and disease.⁷⁷ It is increasingly clear that there are connections between the human microbiome and the immune, endocrine, and nervous systems that may be relevant to a wide array of diseases and conditions, including inflammatory bowel disease, obesity, cancer, and major depressive disorders.⁷⁸

The NASEM report on synthetic biology and biodefense outlined two ways in which the human microbiome could be a target or vector for biological threats. The first method would be to engineer a

commensal (beneficial) bacteria that is part of the human microbiome to produce a harmful compound and then infect humans with this organism. This threat shares many of the features, and limitations, of modifying microbes described above.⁷⁹ The second method would be to use genome editing to target a component of the microbiome directly in order to cause dysbiosis, i.e., “the purposeful perturbation of the normally healthy microbiome.”⁸⁰ In this way, the microbiome could provide a backdoor to attacking key physiological systems that are influenced by the composition and activity of the microbiome.⁸¹

Successfully hijacking the human microbiome, however, faces several challenges. In addition to the difficulties of introducing a new strain into a robust indigenous microbiota, our understanding of how to modify overall microbial community functions and the health impacts of such modifications is still quite limited. In addition, there are significant differences between the behavior of the bacteria that comprise the microbiome in the lab and in their natural habitat. As with all of the possible areas of misuse, however, knowledge about individual components of the microbiome, their interaction with other elements of the microbiome, and the influence they have on different aspects of human health is growing rapidly due to the scientific, commercial, and medical applications that benefit from and drive these advances.⁸² It is also worth noting that disrupting a system may often be easier and require less precise knowledge than restoring a system to a healthy homeostatic state.

Weaponizing Gene Therapy

The ability of genome editing tools to delete, suppress, or amplify the expression of specific genes is a sought after capability for treating monogenic disorders. But this ability could also be used to disrupt the normal functioning of specific biological systems such as the cardiovascular, metabolic, immunological, endocrine, neurological, reproductive, and gastrointestinal systems. In effect, the techniques being perfected for use as gene therapies could also be turned into a genetic weapon.⁸³

Since these physiological systems operate in a delicate balance of homeostasis, there are innumerable ways to disrupt this equilibrium and potentially cause harmful consequences. As the NASEM report on synthetic biology and biodefense noted, “If researchers can create mouse models of particular disease states based on the deletion or addition of particular genes, it follows that if the genomes of human beings could be similarly modified, such modifications could potentially cause a wide variety of non-infectious diseases.”⁸⁴ For example, CRISPR has been used to introduce cancer-causing genes into mice in order to develop an animal model for human lung cancer.⁸⁵ In addition, CRISPR tools that are designed to activate or interfere with gene expression can be used to make epigenetic modifications.⁸⁶ Such tools have already been demonstrated to have a measurable impact on diseases such as diabetes, muscular dystrophy, and acute kidney disease in mouse models.⁸⁷

The immune system is also susceptible to being attacked directly. The suppression of a component of the adaptive immune system, which is tailored to respond to specific pathogens and diseases, could make the target more vulnerable to opportunistic infections or a follow-on biological attack. The immune system could also be tricked into attacking the host, known as autoimmunity. According to the NASEM report, the most worrisome type of tampering with the immune system would be to engineer a hyperactive immune response that could unleash a cascade of systemic responses known as a cytokine storm.⁸⁸

Advances in the neurosciences are dramatically increasing our understanding of the role of neurotransmitters, the chemicals that send messages between the neurons that comprise the brain and nervous system, in regulating physiological functions, cognitive capabilities, and behavior. CRISPR is already being harnessed in basic and translational research in cellular and animal models with the goal of creating personalized therapeutic applications for brain disorders.⁸⁹ At the same time, Diane DiEuliis and James Giordano have also warned that “CRISPR-type gene editors could directly act on genes in the brain to alter neural phenotypes that influence cognition, emotion, and behavior.”⁹⁰

Another, even more worrisome, prospective misuse of genome editing would be to design a biological weapon that could target specific ethnic groups. According to the NASEM report on synthetic biology and biodefense, the combination of population-level genomic data, health metadata, and advanced bioinformatic capabilities, which are being developed in the context of “precision medicine,” could potentially be used in the future to “identify unique vulnerabilities for specific sub-populations and then develop bioweapons tailored to target those vulnerabilities...this approach could be used to develop ethno-specific bioweapons.”⁹¹

Gene Drives as Weapons

A fourth class of biosecurity risks would be the use of gene drives to push deleterious genes into a population.⁹² Gene drives, according to Gabrielle Tarini and Raymond Zilinskas, “pose novel security risks for entomological warfare, agro-sabotage, and ecocide.”⁹³ A gene drive could potentially be used in a population replacement strategy to make disease carrying vectors more dangerous by improving their ability to transmit disease more efficiently, increasing the range of diseases they are capable of transmitting, or expanding their geographic reach. Alternatively, a harmless insect could be altered to enable it to transmit a disease. A population suppression gene drive could be used to target a keystone species in an ecosystem, such as pollinating insects, which could severely disrupt a country's agricultural sector.⁹⁴

Gene drives, however, have several disadvantages that could reduce their effectiveness as a weapon.⁹⁵ First, since gene drives rely on sexual reproduction and successive generations of offspring to spread, they spread slowly, even for animals like insects that have short generation times. Accelerating the pace of gene drive proliferation would require the deployment of large numbers of altered organisms evenly distributed among the target population which would be difficult to do covertly. While this feature may make gene drives unsuitable for use in conflicts that are characterized by *blitzkrieg*-like military activity, it would not be as problematic for governments or groups engaged in attrition warfare. Second, the presence of gene drives in a wild population can be detected since the components of a CRISPR gene drive do not occur in nature and cannot be hidden from modern sequencing methods. However, detecting the presence of a gene drive in the environment would require a dedicated surveillance effort. The effectiveness of such a surveillance system would depend in part on identifying the at-risk species ahead of time and would be constrained by its ability to test a sufficient number of samples obtained from a wide enough geographic area on a frequent enough basis to provide timely warning of the presence of an unauthorized gene drive. In addition, the scientific and financial resources necessary to design and implement such a system would limit its availability to developed nations with strong biotech sectors. Third, it is possible to counter the effects of a malicious gene drive by overwriting unwanted changes with another gene drive. Once a malicious gene drive has been identified, it can be reverse-

engineered to build an **immunizing reversal drive** that lacks the harmful genetic elements and includes guide RNAs that target the original sequence. Whenever the two drives are present in the same organism, the rogue drive system would be overwritten in the germline. The speed with which this type of drive system could spread through and immunize the unaffected population and restore affected populations would depend on how long it takes to detect the malicious gene drive, how long it takes to mobilize the political, scientific, and financial resources to develop an immunizing reversal drive, and the pace at which this drive could be disseminated among the at-risk population. In summary, while certain intrinsic features of gene drives are not well-suited for deliberate misuse under certain conditions, the potential utility of this technology as a weapon also depends on broader political, economic, and technical factors.

It should also be noted that organisms with long generation times, such as humans, cannot be meaningfully affected by gene drives in a short period of time (e.g., a few decades or less). In addition, modern agricultural systems are somewhat resistant to the malicious use of gene drives to directly introduce vulnerabilities into their genomes thanks to seed farms that can provide a reservoir of unaffected seeds and selective breeding programs that monitor and control the genetics of livestock for economic reasons.

Barriers to Misuse

Despite the diverse ways in which advances in genome editing could hypothetically be misused to cause harm, there are significant limitations on the ability of most actors to use genome editing for such purposes, at least at present and in the near future. There are three barriers common to all of these categories of misuse that provide significant roadblocks to groups that are not patient, highly motivated, and well-resourced. Unfortunately, there are also valid concerns that these barriers are being steadily reduced.

First, gaps exist in our collective knowledge about how genotype affects phenotype, and about the mechanisms of gene editing. This impedes knowing what specific gene sequence to edit in which way to have the desired outcome. Consequently, this is a major obstacle to realizing any of these new and improved biological weapons, especially the more novel capabilities of concern.⁹⁶ At the same time, CRISPR provides powerful new capabilities, such as high-throughput screening, that is enabling rapid advances in functional genomics which is closing these gaps in our knowledge. The capacity to engage in a systematic effort to use high-throughput screening or selective conditions and functional genomics to enable discoveries that could be exploited for malicious purposes is for now only within reach for state-run or extensive non-state-sponsored programs. Nonetheless, the tremendous scientific and commercial appeal for improving our understanding of how genotype affects phenotype means that the high-throughput screening methods enabled by CRISPR will inevitably generate reams of dual-use knowledge about pathogenesis, host response, the role of the microbiome, how to modulate the immune and nervous systems, and the genetic determinants of animal, plant, and human health. By enabling high-throughput screening and genome editing, CRISPR's versatility has the potential to create a vicious cycle of exploration followed by exploitation.

Second, while the materials needed to conduct genome editing experiments are widely available, the tacit knowledge and skills necessary to wield these tools effectively are much less common.⁹⁷ Indeed, concerns about amateur scientists using CRISPR in their garage labs to create the next pandemic are often overstated. Despite florid headlines to the contrary, amateurs who report using CRISPR kits frequently do not succeed without consulting someone with more experience in the

field.⁹⁸ Genome editing is a process requiring multiple types of expertise and knowledge from basic lab skills to molecular cloning to bioinformatics. As a genome editing project becomes more sophisticated, the type and level of necessary expertise increases as does the breadth and depth of knowledge required. Third, even if genome editing made it much easier for less-skilled individuals to modify an organism, moving from *in vitro* to *in vivo* applications of genome editing raises new challenges. Transforming a modified organism or GEV into a weapon requires designing it to deliver its payload to the correct tissue or cells, producing it in suitable quantities, maintaining its viability and stability, and disseminating it to the target population. Most GEVs, for example, are designed to be delivered to individuals via intramuscular injection, intravenous injection, or digestion absorption--these are not ideal methods for exposing large numbers of people.⁹⁹ Aerosolization is the most efficient means of disseminating a pathogen across a wide area to infect large numbers of people, but this has been a more difficult capability to master.¹⁰⁰ Such barriers might indicate that at present there are easier paths for developing and delivering biological weapons.¹⁰¹

Advances in the development of adeno-associated viral (AAV) vectors, the most common delivery vehicle for gene therapies, however, raises some potential concerns. Researchers have created a new strain of AAV that is able to penetrate the mucous membrane.¹⁰² This viral vector was developed to serve as the basis for inhalable gene therapy, but it potentially provides a new way to disseminate a harmful genetic payload through aerosolization. In addition, AAVs have been developed that can breach the blood-brain barrier and reach the entire central nervous system which support the development of a neuroweapon.¹⁰³ And finally, aerosol technology and associated large-scale delivery systems are evolving rapidly, so as to become more efficient and effective.

Summary

The growth of the “attack surface” from a biosecurity perspective has expanded dramatically due the open source nature of the life sciences research enterprise, the globalization of its innovators and users, and the increasing integration of biotechnology into the economy. In addition, developments in genome editing have created new potential attack vectors and the means for rapidly identifying additional ones. Indeed, many of these new attack vectors do not involve actual pathogens, but instead genetic constructs and associated means of delivery. Since the current biodefense paradigm is oriented around developing defenses against a short list of pathogens and most defenses are agent-specific, these new attack vectors have⁰the potential to circumvent our current defenses. These new attack vectors raise new attribution challenges as well. Since 2001, the United States has invested heavily in microbial forensics but again, these capabilities are geared towards the analysis and characterization of traditional biothreat pathogens. Although there remain significant barriers to misuse of genome editing in the near-term for states, in the medium-term for skilled groups, and in the longer-term for skilled individuals, the emergence of genome editing and CRISPR in particular poses a new set of challenges to biosafety, biodefense, and biosecurity. Therefore, genome editing presents a significant challenge to the current biosafety and biosecurity regimes which are focused on defending against pathogen threats and regulating the safety and security of federally funded research efforts.

POTENTIAL SECURITY SCENARIOS: ILLUSTRATING GOVERNANCE GAPS AND OPTIONS

Since the 1990s, the United States has invested considerable effort in assessing the risks posed by biological weapons and emerging dual-use technologies in order to better develop effective biosecurity and biodefense policies. Notable scientific developments of the past decade — including the artificial synthesis of the poliovirus, the resurrection of the 1918 flu virus, the creation of the first self-replicating “synthetic” cell aided by DNA synthesis, and the gain-of-function experiments that enhanced the transmissibility of the H5N1 flu virus — have raised similar concerns currently being voiced about genome editing. Concerns related to each of these research projects presented the opportunity and obligation to reconsider the governance landscape. Similarly, advances in genome editing have illuminated the need to examine the current state of governance, identify gaps and areas for improvement, and provide new governance options, while ensuring the appropriate balance between promoting safety, security, and innovation.

This section illustrates governance gaps and options in four categories. Provided within each of these categories are scenarios that were developed by drawing upon the study’s workshops, input from subject-matter experts, and supplemental research and analysis. The scenarios have been grouped across these four main categories, but elements of each could appear in other categories.

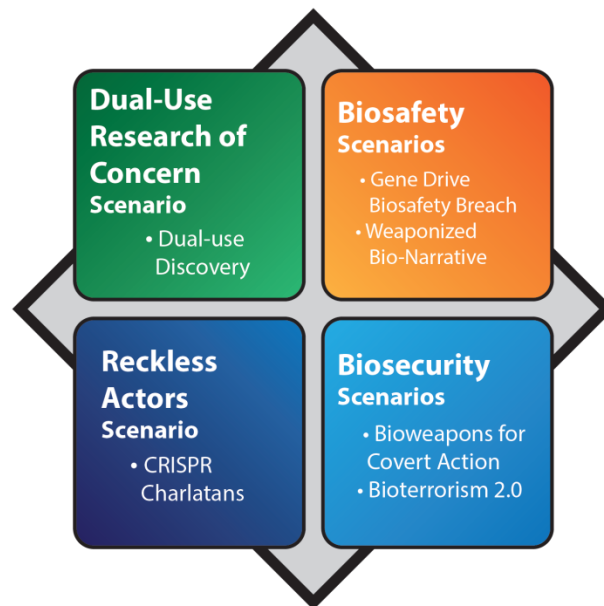


Figure O. Areas of security concern and corresponding scenarios.

The scenarios illustrate the complexity of vulnerabilities and risks, gaps in current policy and practice, and the ecosystem of actors that must be involved to manage the changing security landscape. The scenarios are designed to highlight risks and gaps that may not be immediately obvious. These non-intuitive scenarios are intended to underscore how the evolving security landscape will involve a wide range of stakeholders who need to be engaged and empowered in order to contribute to crafting security-relevant solutions. The scenarios are structured around concrete, yet hypothetical, examples. Mindful of potential information hazards, they have been written to be plausible, but not capable of enabling misuse. The scenarios do not represent a comprehensive set of concerns, nor are they necessarily the most important, and they are not intended to be predictive. Instead, they are tools for illustrating gaps between current biosecurity policies and the challenges that emerging genome editing capabilities may pose in the near future.

Advances in genome editing have illuminated the need to examine the current state of governance, identify gaps and areas for improvement, and provide new governance options, while ensuring the appropriate balance between promoting safety, security, and innovation.

Scenario Selection Criteria

- Illustrate the complexity of vulnerabilities and risks
- Illuminate gaps in governance
- Represent a variety of potential actors
- Represent a variety of actors' motivations and goals
- Represent a variety of technical capabilities
- Represent diverse use of the technology in multiple areas of interest
- Must be credible and plausible, but not necessarily feasible, to avoid information hazard
- Illuminates broader strategic, technological, and policy changes that are shaping the biosecurity landscape

Each scenario is coupled with examples of policy options that illustrate a range of representative approaches that could address the identified governance gaps. The options presented are not wholly conclusive, nor do they preclude other options for governance or actors who could implement such options. Finally, the scenarios offer background and context that is intended to display how the discussion and debate around genome editing, and CRISPR in particular, illuminates broader strategic, technological, and policy changes that are shaping the biosecurity landscape.

Security Scenarios

Reckless Actors

Scenario: CRISPR Charlatans

This scenario illuminates consumer health and safety issues arising from the use of genome editing in the development of loosely regulated products. The scenario revolves around a reckless, profit-driven actor who develops and markets products created with genome editing that could have serious adverse effects for patients.

Dr. Nandina Gupta had never seen anything like it before in her twenty years of being an officer in the Epidemic Intelligence Service, the Center for Disease Control's famed "disease detectives." Sixteen middle-aged patients presented at a hospital in Florida over the course of two weeks exhibiting severe symptoms of inflammatory bowel disease (IBD). IBD is the chronic inflammation of the digestive section, and onset of IBD can be the result of an overactive immune system. Similar cases quickly emerged around the country. Although the condition did not appear to be contagious, the surge in cases, especially among younger patients, and their occurrence in geographic clusters, was alarming. It took Dr. Gupta and her team a week to determine the source of the outbreak: a new dietary supplement called Immunio. By this time, over 50 patients had shown signs of an overactive immune system.

Immunio was just one of many new probiotics that had emerged in recent years to capture part of the projected \$5 billion global market for products designed to improve the immune system and digestive health.¹⁰⁴ The strong interest in probiotics, or live microorganisms that provide a health benefit to the host, was driven in part by growing concerns about the spread of antibiotic-resistant bacteria and new discoveries enabled by NIH funding.

Immunio was produced by the startup HealthBiotics. Like other probiotics, Immunio was composed of so-called "good" bacteria that are commonly found in the human gut, in this case a specific *Lactobacillus acidophilus* strain. What made Immunio different, and ultimately dangerous, was that the company had hired a third-party contract research organization that used CRISPR to insert a complex gene cassette into the probiotic *Lactobacillus* strain. Research indicated that the cassette expressed the immune regulatory protein IL23. The intended purpose was to induce expression of the protein with a separate antibiotic trigger in situations demanding the presence of effector, regulatory T lymphocytes in the colon, such as certain kinds of intestinal bacterial infection. Although expression of the protein was supposed to be tightly controlled and dependent on ingestion of the antibiotic, the protein expression control mechanism was faulty, and high levels of IL23 were produced constitutively, resulting in fulminant colitis, a potentially life-threatening condition that affects the colon.

Although HealthBiotics used cutting-edge genome editing techniques to engineer their probiotic, they avoided the lengthy clinical trials and other burdensome aspects of the Food and Drug Administration's (FDA) licensing process for new drugs by marketing their product as a dietary supplement. HealthBiotics successfully avoided having Immunio labeled as a drug and subject to stronger regulatory oversight by the FDA because it did not make any claims that the product was intended to "diagnose, treat, cure, or prevent any disease."

By the time that Immunio was pulled from the market, 179 people had been diagnosed with symptoms related to an overactive immune system. Thankfully, none of those affected died. The survivors faced continuing medical challenges and a long-term recovery process. The public and political backlash was not limited to HealthBiotics and Immunio, but the entire field of probiotics and gene therapy also suffered.

Takeaways

- **New Products and Delivery:** A range of products could be developed using genome editing, and some are likely to be delivered in new ways that can be less well-regulated. For example, dietary supplements are subject to less federal oversight than drugs.
- **Unclear Regulatory Status:** Genome edited products can have unclear regulatory status that companies can exploit. For example, the regulatory status of genetically engineered probiotics is unclear.
- **Risks to Consumers:** Reckless actors taking advantage of loosely regulated markets, including dietary supplements and health clinics marketed outside medical regulations, can pose risks to health and safety.
- **Risks to the Industry:** Products that pose risks to public health may also have negative consequences to broader fields of science and applications of genome editing. For example, adverse reactions to new drugs has caused dramatic loss in funding for basic research and development.
- **Complex Networks and Vulnerabilities:** Actors without biotechnology skills can contract specialists to carry out relevant work. Lack of oversight in the transactions in these industries also introduces points where materials and information can be potentially acquired by those with malicious intent, or where vulnerabilities can be introduced.

Options for Protecting Consumer Health and Safety

- **Regulatory Oversight and Pathways:** The FDA regulates food, dietary supplements, and drugs differently, with comparatively looser regulations on dietary supplements. The FDA could create a single regulatory pathway for probiotics to promote and ensure product safety.
- **Industry Engagement and Incentives:** Producers of dietary supplements could voluntarily work with the FDA in establishing a framework and labeling practices that accurately label the safety of their products. Probiotics with a long and proven track record of health benefits could be labeled accordingly. Leaders in the industry who comply with such labeling, perhaps through a certification of compliance, could be potentially rewarded by increased consumer trust and market share.
- **Regulatory Standards:** As the FDA reviews its guidelines for how industry measures and labels live microbial quantity in dietary supplements, it could require manufacturers to

provide detailed labeling information on each bottle of supplements indicating the organism strains and their number per serving. This could help safeguard against manufacturer adulteration of the products and contamination during manufacturing.

- **Regulatory Capacity:** The Federal Trade Commission (FTC) could increase its capacity to monitor direct-to-consumer marketing of unapproved gene edited products in order to detect and halt large-scale initiatives similar to what we have seen in the case of stem cells. Increasing capacity for oversight requires addressing longstanding issues of sufficient resources for oversight.

Background and Context: Loosely Regulated Markets

A range of products could be developed using genome editing that are delivered in new ways that are less well-regulated. Two examples are in the areas of dietary supplements and non-medical therapies.

Probiotics

The Food and Drug Administration is responsible for the regulation of dietary supplements under the Dietary Supplement Health and Education Act of 1994. The FDA's role begins once a product is introduced into the marketplace, where the agency is responsible for identifying and removing hazardous supplements and supplements that have been adulterated. Federal law does not require that supplements be proven safe before being brought to market. Manufacturers of dietary supplements are responsible for ensuring that their products are safe and that their claimed health benefits are supported by evidence, but they are not required to provide this information to the public or have it scrutinized by the FDA.¹⁰⁵ Dietary supplements cannot claim that the product is intended to diagnose, treat, cure, or prevent any disease. Many brands of supplements have been found to contain pharmaceutical adulterants, including prescription medications, withdrawn medications, and unapproved drugs, posing a risk to human health.¹⁰⁶ Although the FDA has not approved any probiotic as a biotherapeutic product, there are probiotics legally available as dietary supplements. At present, the FDA is reviewing policy guidelines for how industry measures and labels live microbial quantity in dietary supplements.¹⁰⁷ The FDA requires manufacturing compliance for supplement producers, but non-compliance is a persistent issue.¹⁰⁸ The risk of exploitation is likely highest for uses of genome editing that are not marketed as medical interventions or products, but as cosmetic or dietary.

Loosely Regulated Clinics and Therapies

Just as unscrupulous doctors have exploited regulatory loopholes and lax enforcement by the FDA to peddle unapproved stem cell treatments, a similar situation could arise with unapproved gene therapies.

Until recently, the proliferation of stem cell clinics has outpaced the enforcement of existing regulations and the development of new regulations.¹⁰⁹ Stem cell "treatments" have resulted in a range of adverse effects from blindness to death.¹¹⁰ In August 2017, vials of smallpox vaccine were

seized from a stem cell clinic in California that was mixing the vaccine with a patient's stem cells and then injecting the mixture back into the patient's tumors. This procedure could potentially cause a deadly inflammation and swelling of the heart.¹¹¹

Stem cell clinic operators have avoided regulatory oversight by claiming that their products fall under an exception in Food and Drug Administration (FDA) regulations for biological products that are "minimally manipulated" and for autologous treatments that are taken from and put back into the same patient during a single surgical procedure. At the same time, many of these clinics also offer treatments based on stem cells from sources other than the patient and therefore should not be exempt from regulatory oversight.¹¹² Clinics have even enrolled so-called "patient-funded studies" on Clinicaltrials.gov as a way of projecting a false image of legitimacy.¹¹³ The Bureau of Consumer Protection of the FTC recently levied a partially suspended fine of \$3.31 million on two stem cell clinics engaged in deceptive advertising practices promoting unproven treatments.¹¹⁴ This is the first time the FTC has done so, despite the fact that hundreds of stem cell clinics engage in direct-to-consumer marketing in the U.S.¹¹⁵

There have also been a small number of cases of so-called biohackers publicly injecting themselves with genetically engineered compounds that they claimed could treat HIV, cure herpes, or foster the growth of larger muscles. In addition, a company called The Odin sells kits that contain CRISPR constructs designed to knock-out a human gene that regulates muscle growth. By itself, the kit is not sufficient for conducting genome editing, much larger quantities of purified DNA would be necessary as well as a method for inserting the DNA into the genome and delivering it widely across tissues.¹¹⁶ Another company, the ill-fated Ascendance Biomedical (which has re-emerged as the Transcendence research collective) attempted to develop a "decentralized" drug testing arrangement. The arrangement would have skirted FDA regulations by selling the gene therapies they were developing to individuals, who would administer it themselves for research purposes and not for therapeutic application.¹¹⁷

Since the FDA considers any use of CRISPR-Cas9 genome editing in humans to be gene therapy, and therefore subject to regulatory oversight, it has warned that the sale of gene therapy products intended for self-administration, and "do it yourself" kits designed to produce gene therapies for self-administration, are against the law.¹¹⁸ Ascendance Biomedical initially resisted the FDA notice, but it has since gone out of business. The Odin's kit is still for sale, although it now comes with a disclaimer telling purchasers not to inject it or use on humans. While this type of self-experimentation may be bad for the health of the practitioner, it does not pose a serious threat to public health. More problematic would be the development of large-scale initiatives to provide unapproved genome edited products to the public as was seen in the case of stem cells. Another potential implication is that the lack of oversight in these markets provides more opportunities for acquisition of information and materials, such as gene therapy delivery vectors, that could be rate limiting steps in the development of malicious applications.

Dual Use Research

Scenario 2: Dual-Use Discovery

This scenario illuminates how research that is enabled by genome editing exposes gaps in the oversight of dual-use research of concern (DURC), including a narrow focus on pathogens and exemption of privately funded research. This scenario revolves around an agriculture biotech company using genome editing research to develop applications with potentially significant consequences for human health.

Agrobite, an agricultural biotech startup in Iowa, is using genome editing to develop a breed of pigs that is resistant to porcine parvovirus. The virus causes a high rate of fetal deaths and stillbirths in pregnant female pigs. Although a vaccine exists for the disease, there are signs that it is losing its effectiveness.¹¹⁹ Previous research had demonstrated that porcine parvovirus is dependent on a specific receptor (cell surface protein) of porcine macrophages--large white blood cells--for the virus to infect cells.

Experiments at Agrobite have demonstrated that using CRISPR to knock out this receptor entirely renders the cell resistant to infection with parvovirus but also impairs macrophage normal functioning. To maintain macrophage function, Agrobite researchers tried to replace the porcine receptor with orthologs--genes in different species that evolved from a common ancestral gene--from other species. They found that the human receptor was the only one that produced a structurally similar protein that did not interact with the virus. They discovered that this human-porcine hybrid macrophage maintained resistance to infection with parvovirus, retained its normal functions, and that this trait could be inserted into pig zygotes for germline editing. Once the FDA and USDA finalizes rules on how it will regulate animals modified with genome editing, Agrobite plans on commercializing its parvovirus-resistant pigs.

In the meantime, the researchers have submitted their study for publication in a peer-reviewed scientific journal. One of the peer reviewers raises concerns about the potential for the parvovirus to adapt to the new receptor that uses a human genetic sequence, thereby turning this animal disease into a potential human pathogen. The reviewer was made aware of this issue because another research group, working on this same issue, identified the risk and noted it in a recently submitted manuscript to the journal. But because of the often guarded nature of scientific research, Agrobite was unaware of this group's research and the risk they identified, and they failed to identify this risk themselves. The journal reaches out to the National Science Advisory Board for Biosecurity (NSABB) for advice, but they are told that the board's mandate does not include reviewing individual articles that represent dual-use concerns. NIH, FDA, and USDA also decline to provide advice since the research was conducted with private funding and did not involve one of the Tier 1 pathogens on the list of agents subject to dual-use research oversight. The company's board is divided on how to

proceed, but given the uncertainty on the potential risks of generating a new zoonotic disease and their liability, Agrobite temporarily shelves the research.

Takeaways

- **Proliferation of Dual Use Dilemmas:** Advances in biotechnology, which are enabled by genome editing, are increasing the complexity and sophistication of research that poses potential dual use risks. These risks are context-dependent and often difficult to assess, including for indirect effects on human health such as in the agricultural sector and conservation.
- **Ad-hoc Management Processes:** Dual use oversight processes vary by institution (e.g., research institutes, journals, funders, and others) and largely rely on an ad-hoc process of expert consultation. Experts inconsistently identify risks, and often disagree on the scale of risks.
- **Limited Scope of Oversight:** While the intention of current Dual Use Research of Concern policies was to reconsider their scope over time, in practice the policies remain narrowly focused. Privately funded research is exempt from compliance with NIH Guidelines and dual-use research oversight.
- **Risks of Regulatory Uncertainty:** Lacking clear pathways for guidance on dual use research outside of the scope of current policies, stakeholders (e.g., researchers, funders, publishers, and others) must independently assess their liabilities, which can lead to inconsistent strategies and impede research that could be beneficial if appropriately managed.

Options for Improving Dual-Use Research Oversight

- **Reconsidering Scope of Oversight:** The scope of U.S. dual-use research oversight could be revisited and potentially broadened to include all life sciences research that engages in experiments of concern beyond the current limited set of pathogens. Mechanisms to ensure regular reconsideration of the scope of dual-use research oversight could be instituted.
- **Enhancing Oversight of Privately Funded Research:** Legislation could be introduced in the U.S. Congress to create a comprehensive, nationwide dual-use research oversight system that would include public and privately funded research in the life sciences.
- **Practitioner Engagement:** Federal agencies that fund life sciences research in the United States, in conjunction with scientific societies and professional associations, could lead a campaign to educate the communities they interact with about dual-use research and how best to conduct their research responsibly. Among the options to institutionalize education about dual-use issues within the life sciences community, the NIH could include this topic in its Responsible Conduct of Research training, which includes the “ethical principles in the performance of all activities related to scientific research.”
- **Applied Biosafety and Biosecurity Research:** Designing adaptive oversight systems to keep pace with changes in technology is enabled by applied research on policy implementation in concert with policy development. More funding could be put towards enabling this type of work across government and nongovernmental organizations, including universities and research consortia, in line with the National Biodefense Strategy’s emphasis on applied biosafety and biosecurity research.¹²⁰

Background and Context: Dual Use Research of Concern Oversight

Oversight of dual-use research of concern has two important limitations. First, there is a narrow focus on pathogens, and there is an expanding number of applications of genome editing to a variety of non-pathogenic organisms. Second, privately funded research is exempt from oversight.

In 2012 and 2014, the U.S. government issued policies to govern dual-use research of concern conducted by public and private research institutions. DURC was defined as “life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.” While the DURC oversight policy highlighted the need to update the scope over time, in practice the scope of the current policy has remained narrow, including two important limitations.

First, oversight is applied only to seven types of experiments conducted on one of fifteen pathogens or toxins that are regulated under the Federal Select Agent Program (FESAP).¹²¹ FESAP is designed to prevent unauthorized access to a list of designated pathogens and toxins (called select agents) that are considered to present the greatest risk of deliberate misuse and are subject to strict security requirements. A second limitation is that DURC oversight only applies to public or private research institutions that receive Federal funding for life science research. This policy also applies to foreign research institutions that receive U.S. funding for DURC research. These institutions are required to establish an Institutional Review Entity (IRE) to implement the DURC policy. Institutions, including companies and independent research institutes, that conduct life sciences research and do not receive any Federal funding are exempt from this oversight.

In 2017, in response to studies on avian influenza that potentially fell outside of the scope of the policy, the Office of Science and Technology Policy (OSTP) in the White House and the Department of Health and Human Services (HHS) issued additional guidance on research involving the creation, transfer, and use of potential pandemic pathogens with enhanced virulence and/or transmissibility: The Policy on Potential Pandemic Pathogen Care and Oversight (P3CO). This new policy is notable for a few reasons. First, the policy is not based on lists of experiments or on specific pathogens, as in the case of DURC policy, but instead takes a risk-based approach that focuses on the attributes of modified organisms. While the identity of the starting organism is central to the original DURC policy, this new framework emphasizes the importance of an organism's' properties once the experiment is over. Second, the policy is more prescriptive about the criteria used to review research. For example, the new HHS policy calls for an assessment of whether there are “no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than does the proposed approach.” Such considerations were implicit in previous DURC policy in the context of risk mitigation, but this new framework makes this trade-off explicit. In addition, the HHS policy includes consideration of whether the research is “ethically justifiable.” Previous guidance for dual-use research of concern was focused strictly on scientific criteria for assessing the risks and benefits of dual-use research.

Genome editing, alongside other advances in biotechnology, poses a fundamental challenge to the way that dual-use research oversight in the United States is conceived and implemented on two levels. First, beginning with the 2004 Fink report, a core assumption has been that the greatest source of concern in dual use research was modifying pathogens to be more dangerous.¹²² The expanding number of applications of CRISPR to a variety of non-pathogenic organisms of scientific and commercial interest means that the knowledge and expertise to transform an easily accessible,

but relatively harmless, agent into a more dangerous one is increasing. Furthermore, and more importantly, CRISPR creates new research opportunities that could generate significant dual-use risks that do not involve any pathogens whatsoever. For example, the use of CRISPR to study the genetic sources of cancer, how the microbiome maintains homeostasis, or the genetic determinants of neurological disorders, all could generate dual-use knowledge that could be used to cure or cause disease. Methods of delivering genome editors, via a viral vector or some other option, that are able to target specific organs or be delivered more easily also provide a dual-use capability. The adoption of CRISPR by broad swathes of the life sciences research community highlights the need to build awareness of potential risks across the entire community, instead of singling out a small subset of researchers. Indeed, the Fink report anticipated that advances in science and technology would raise new dual-use research concern. Therefore, the report recommended that the entire life sciences enterprise be subject to oversight and participate in awareness raising and education activities involving dual-use research.

Second, both the DURC and potential pandemic pathogen policies exempt institutions that do not receive Federal funding. While Federally-funded universities are the leaders in basic research involving genome editing, private entities, including corporations and philanthropies, are playing an increasingly important role in conducting and funding basic and translational research.

For the first time since the end of World War II, private funding of basic research has outpaced government funding.¹²³ The exemption of privately funded life sciences research from dual-use oversight is a large and growing loophole.

In 2017, leading synthetic biology companies, include several that specialize in genome editing, collectively raised more than \$1.7 billion in investment.¹²⁴ In 2018, the CRISPR startup Editas raised \$120 million from private investors including Bill Gates and Google Ventures.¹²⁵ The rise of crowdfunding platforms, such as Experiment and Consano, are another potential source of funding for researchers in the life sciences. For example, the Glowing Plant project to create bioluminescent plants received \$484,000 in less than two months on Kickstarter.¹²⁶ In 2018, a private company funded the first-ever synthesis of an orthopoxvirus, a genus of viruses which includes the variola virus that causes smallpox.¹²⁷

In addition, these private research institutions and funders represent another group that would benefit from awareness-raising and education about dual-use issues. To date, the debate about the risks of genome editing have focused heavily on the ethical issues that arise from the germline editing of humans. Researchers who work with gene drives, however, have tried to address biosafety and biosecurity concerns proactively, with mixed success. It is unclear to what extent other elements of the genome editing community, including those developing these tools, those using the tools, and those selling the tools, have considered the potential misuse of their products. Thus, there is a strong need for an awareness raising campaign to educate the community about potential risks and ways to mitigate them without unduly infringing on research and beneficial applications.

Biosecurity

Scenario: Bioweapons for Covert Action

This scenario illuminates how research involving genome editing may enable new and improved biological weapons with different strategic uses. It revolves around a state using existing published research to overcome technical bottlenecks.

The authoritarian leader of West Mosap is facing a crisis. An economic recession and rampant corruption have led to a sharp increase in social unrest. Her crackdown with mass arrests, torture, and extrajudicial killings have resulted in condemnation from the international community. A senior official in her government, who has inside information on the regime's corruption and human rights abuses, recently defected to a neighboring country. The leader can't afford to allow the defector to rally international support against her. The leader also can't afford to allow a botched assassination attempt to create an international crisis. The leader tasks the head of her special security service with killing the defector in a way that appears to be caused naturally and can't be linked back to West Mosap. The head of the security service considers using a nerve agent like the one that North Korea used to kill Kim Jong Un's half-brother or that Russia used in an attempt to kill the double agent Sergei Skripal. In both cases, however, the use of such an exotic poison was detected relatively quickly and immediately linked to the state sponsor.

Instead, the security chief chooses to use a new means of assassination that leverages the latest advances in biotechnology. Her scientists have developed a genetic weapon that triggers a severe neurological response that mimics a natural condition. This weapon represents a novel biological method for covert assassination. To overcome technical obstacles that previously hampered the weapon's delivery, the team relied on published research on the use of viral vectors that can cross the blood-brain barrier to target specific tissues in the brain for therapeutic purposes. The weapon is successfully deployed in a clandestine manner leading to a steep decline in the defector's memory and cognitive functions and eventually his death. The subsequent investigation is stymied as public health, medical, and law enforcement authorities attempt to establish the cause of death. With a successful first use, the leader considers what other types of effects could be delivered more widely without detection using these new tools.

Takeaways

- **Weapons with Varying Strategic Uses:** Genome editing can enable the creation of new and improved biological weapons. These new weapons may not be designed for use in a conventional military conflict, but to serve different strategic uses, including as tools for clandestine assassination or for use in counterterrorism or counterinsurgency operations. Such weapons may exacerbate existing, or create new, biodefense vulnerabilities.

- **Leveraging Public Research:** There is an increasingly large pool of legitimate biotechnology research that states may be inspired by and use directly to overcome technical bottlenecks and barriers.
- **Challenges to International Norms:** Development and use of new types of biological weapons using genome editing could erode existing international norms against their development and use.
- **Problems of Detection and Attribution:** New weapons that have insidious effects may be increasingly difficult to detect, including if applied more systematically across populations. These weapons could exacerbate the existing challenges of determining who is responsible if their use is ever detected.

Options for Strengthening Biological Weapons Norms

- **Science and Technology Review:** States parties to the Biological Weapons Convention (BWC) could establish a mechanism for conducting regular, systematic reviews of science and technology relevant to the treaty. States parties could also agree to increase the capacity of the Implementation Support Unit (ISU), the body that administers the treaty, to help organize and conduct such reviews. These activities could also serve to compare and develop systems for review and notification of potential dual use research.
- **Clarifying Coverage of BWC:** At the next Review Conference in 2021, the states parties could clarify that the definition of “other biological agents” mentioned in Article 1 of the treaty includes organisms modified with gene drives and genetic constructs.
- **International Engagement:** The ISU could be provided with additional resources to work with partnering organizations to conduct outreach, education, and awareness raising activities with the international life sciences research community. Such partnerships could ensure as wide as possible appreciation among the life sciences research community of the norms against the development and use of biological weapons.

Context and Background: The Biological Weapons Convention

Developments in the life sciences may overwhelm states parties’ capacity to assess the impact on the objectives of the Biological Weapons Convention.

Biological Weapons Convention

The 1972 Biological Weapons Convention was the first international treaty to ban an entire class of weapons. Article 1 of the treaty prohibits the development, production, or acquisition of “microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.” Since the signing of the treaty coincided with the birth of the biotechnology revolution, states parties have sought to ensure that the treaty remains relevant in the face of developments in science and technology. Since 2006, the states parties have reaffirmed at the quinquennial Review Conferences that “Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention.” In 2018, the BWC convened a meeting of experts who spent two days reviewing developments in science and technology relevant to the treaty, with a focus on genome editing. Several states presented working papers on the relevance of genome

editing to the BWC and exchanged their views on the importance of this technology. This limited discussion highlighted that the speed and magnitude of advances in the life sciences, especially in the field of genome editing, are overwhelming the regime's capacity to assess their impact on the objectives of the treaty. One coupled challenge is that the body that administers the treaty, the Implementation Support Unit, operates with a very limited budget and staff, and is under constant financial strain to secure funds owed by States Parties.

Scenario: Bioterrorism 2.0

This scenario illuminates biodefense vulnerabilities that can emerge from an increasingly complex global ecosystem of materials and service providers for biotechnology research. It involves a terrorist group that takes advantage of commercially available resources and a lack of customer screening to use genome editing to convert non-pathogenic bacteria into a biological weapon.

The New Dawn is a white supremacist and millenarian group dedicated to purifying society of “undesirable” elements. Instead of engaging in random acts of violence or symbolic acts of terrorism, New Dawn is pursuing an alternative method to achieving their goal of a white ethno-state. The leaders of New Dawn prey on talented, lonely individuals, particularly PhD students and post-doctoral researchers, whose social and professional achievements have not lived up to their expectations and who hold strong grievances against minority groups or society in general.

The group decides to combine their members' limited expertise with CRISPR, and an easily acquired non-pathogenic bacteria, to create a new biological weapon. The group orders what they need to set up a rudimentary but functional lab from a variety of domestic and overseas suppliers. The backbone of their biological weapon is the innocuous *E. coli* bacteria, which can be found in the environment and the gut of humans and animals. *E. coli*'s hardiness, versatility, and ease of handling have made it the favorite microbial model organism for biologists and a workhorse for the biotech and pharmaceutical industries. These same properties also make these bacteria well-suited for the purposes of New Dawn. At first, the group tries to use CRISPR to modify a lab strain of *E. coli* to produce botulinum toxin, the most lethal toxin known to humans. One of the group's members is able to obtain a synthetic copy of the gene coding for the toxin from a DNA synthesis firm in Asia that does not conduct sequence or customer screening. Nonetheless, this effort is unsuccessful due to the difficulty of engineering a new metabolic pathway for the bacteria to produce the toxin.

The group's next attempt to develop a biological weapon is to engineer a different strain of *E. coli*, called O157:H7. While most strains of *E. coli* are harmless, a few can produce toxins. Due to their low infectious dose and their ability to spread through contaminated food and water, these strains can cause outbreaks of food poisoning. *E. coli* O157:H7 is one the more dangerous strains of the bacteria since it produces the shiga toxin that can cause severe food poisoning with a lethality rate of 5-10%. The group hopes to engineer O157:H7's existing metabolic pathway to increase the amount of shiga toxin produced by the bacteria, with the aim of inducing high fatality rates in those who consume food contaminated with the bacteria. The group plans on disseminating its super-toxin producing bacteria by contaminating food and beverages in restaurants in predominantly minority neighborhoods.

Takeaways

- **Increasingly Complex Global Industry:** There is an increasing number and diversity of providers of materials and services supporting biotechnology research.
- **Inconsistent Oversight Standards:** Customer and order oversight and screening standards exist in some cases, such as in the DNA synthesis industry, but these do not cover the full global market. Other suppliers in the industry, such as genome editing software or reagent suppliers, or companies that provide on-demand biological engineering services, often lack any screening standards.
- **Experiments Evading Oversight:** Using genome editing to modify non-pathogenic bacteria to be more dangerous can circumvent oversight under the Federal Select Agent Program because the bacteria do not appear on the select agents list.
- **Insider Threats:** The relatively high level of skill required to successfully conduct biotechnology research means that there are potential risks posed by insiders.

Options for Improving Oversight of Biotechnology Goods and Services

- **Industry Oversight Standards:** The U.S. government could work with providers of biotechnology goods and services (including those related to genome editing, such as gRNA, CRISPR Cas proteins, bioinformatic tools, and vectors) to establish voluntary guidelines that include “know your customer” standards similar to those employed by the IGSC, especially for items that pose a higher risk of misuse (such as human oncogenes and vectors that are inhalable or can cross the blood-brain barrier). The U.S. government could also encourage the genome editing industry to adopt a standard to use only goods and services provided by companies that adhere to customer screening standards.
- **Funding Incentives for Industry Oversight:** The U.S. could require recipients of government funding for life sciences research to purchase from companies that demonstrate a level of customer and order screening (e.g., DNA only from suppliers that meet IGSC standards and genome editing vectors or reagents from companies that have customer screening standards). Private funding bodies could, as a condition of funding, also require similar standards for researchers to purchase screened DNA.
- **Industry and International Engagement:** The U.S. government could work with other countries with large biotechnology industries, such as China, to co-develop standards, possibly via support for an international standards consortium.
- **Incentives for Research Organizations:** Journals and professional societies could only publish or accept for presentation research that has meet screening standards.
- **Applied Security Research:** The U.S. government could continue and expand sponsored research on methods to increase the effectiveness and reduce the cost of screening. One option for DNA synthesis screening is to develop a curated database of “sequences of concern.”¹²⁸ Another is to explore a sequence screening upgrade that utilizes one-way encryption to screen sequence fragments through an international network of cloud-based servers. The database would be populated with crowdsourced suggestions provided “by an international team of experts familiar with information hazards, each of whom would remain ignorant of sequences added by the others,” but would remain private to protect proprietary information.¹²⁹

Context and Background: Synthetic DNA Screening

The International Gene Synthesis Consortium is comprised of leading DNA synthesis firms who voluntarily screen customers and their ordered sequences.

Synthetic DNA Screening

The field of synthetic biology is characterized by a mix of governance measures. In 2009, a group of leading DNA synthesis firms formed the International Gene Synthesis Consortium and announced that they were voluntarily adopting customer and sequence screening standards.¹³⁰ The IGSC is comprised of 12 DNA providers, and it collectively accounts for 80% of the global market in DNA synthesis.¹³¹ As part of the screening process, orders are compared against a database of nationally and internationally regulated pathogens and toxins to determine if any ordered sequence poses a security risk. If the automated screening system detects a close match between an ordered sequence and a regulated agent, the order and the customer are scrutinized manually.¹³² Based on this manual analysis, the order can be filled, the company can reach out to the customer for more information, the order can be cancelled, or the company can contact government authorities. In 2015, manual screening analysis and customer follow-up cost on average \$14.35 per order, which represented approximately 1.5-3% of the total order cost. As the cost of DNA synthesis continues to decrease, and screening costs remain relatively stable at present, manual screening will constitute a larger percentage of overall cost.¹³³

Members of the IGSC share information on a regular basis within the confines imposed by the need to safeguard proprietary business information. Implementation of the IGSC's standards, however, are at the discretion of each company, and there is no mechanism for the consortium or its members to assess the degree to which members are complying with the consortium's standards.

A gap in the standards that IGSC has yet to address is the potential for non-pathogenic coding DNA sequences, which are not covered by current screening methods, to be synthesized and used nefariously. For instance, genes relating to ecosystem niche habitat preference for a harmless organism could be ordered from a DNA provider. Using CRISPR, the genes could then be inserted into an esoteric pest species to modify or expand its range. This could result in potentially serious economic or ecological effects. This gap is especially important in the context of target selection for gene drives.

In parallel with the industry's development of codes of conduct, the U.S. Department of Health and Human Services (HHS) crafted voluntary guidelines for U.S.-based DNA synthesis providers that were published in 2010. These guidelines detail customer screening measures, standards for sequence screening, and the process for raising concerns with the appropriate government authorities. HHS recommendations only cover double-stranded DNA longer than 200 base pairs; they do not cover short oligonucleotides (single-string DNA).¹³⁴ In addition, there is no mechanism for assessing whether companies, based in the United States or elsewhere, are complying with the HHS guidance.

Biosafety

Scenario: Gene Drive Biosafety Breach

This scenario illuminates the potential for accidental release of new types of biological organisms created through genome editing, as the number and sophistication of labs using these techniques grows. It revolves around the release of a self-propagating gene drive organism from a research laboratory.

Monique is a second-year postdoctoral researcher at National University, where she's working on cutting-edge gene drive research in the *Ceratitits capitata*--Mediterranean fruit fly (aka Medfly). The goal of the research is to develop a gene drive that will suppress the Medfly population by reducing the number of viable offspring. Suppression is desirable because the species is extremely destructive to nuts, fruits, and vegetables, and causes significant economic damage to the commercial agriculture sector.¹³⁵ In addition, the Medfly is an invasive species that has spread from the Mediterranean to the Middle East, Africa, Australia, Hawaii, and South and Central America. There is a risk of the fly further spreading to California, Texas, and Florida.¹³⁶

The lab receives U.S. federal funding and must therefore follow the National Institute of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines).¹³⁷ As required by the NIH Guidelines, the university's Institutional Biosafety Committee (IBC) has reviewed the lab's biosafety protocols and practices in order to ensure the safety of researchers and to safeguard against an accidental release of organisms. But because the IBC members lacked specific expertise in gene drive technology, they were unfamiliar with the best biosafety practices for gene drive experiments. The best practices are elective as they currently lack government-issued authority because they fall outside the NIH Guidelines.¹³⁸ In addition, while the NIH Guidelines specify containment requirements for numerous organisms and experiments, they do not at present offer such guidelines for gene drive experiments. Nevertheless, the lab has containment facilities and protocols consistent with the NIH Guidelines' Biosafety Lab-2 (BL-2) level and has voluntarily applied the American Society of Tropical Medicine and Hygiene (ASTMH) Arthropod Containment Guidelines ACL-2 level of containment.

For purposes of scientific comparison, the lab has Medflies that are both wild-type (i.e., non-gene drive) and those containing the gene drive. Both are housed at the ACL-2 level. Recently, the wild-type strain of Medfly has been contaminated with gene drive due to Monique accidentally moving some gene drive Medflies to the wild-type container. A collaborating lab has requested shipment of the wild-type Medfly. Because that lab only houses nontransgenic wild-type flies, they are kept at an appropriate lower level of containment (i.e., BL-1/ACL-1). Unaware of the contamination, Monique's lab manager ships the gene drive flies. Given the lower level of containment, several of the gene drive Medflies escape from the lab. Thankfully, the lab is located in New England. Given the harsh winter and Medflies inability to survive such cold temperatures, the escaped flies are not expected to

survive and will likely not reproduce with any native flies, which means the gene drive is unlikely to spread.¹³⁹

Takeaways

- **Diffusion of Gene Drive Technologies:** The potential for self-propagating gene drive organisms to be used to address persistent challenges in global health, and pest and invasive species control, has led to many more groups experimenting with its uses. As the number of groups increases, so does the possibility for accidental release.
- **Gaps in Biosafety Guidelines:** Despite development of guidance by the scientific community, the formalization and dissemination of such standards often occurs slowly. There remain gaps in the NIH biosafety guidelines for experiments involving gene drive organisms.
- **Gaps in Shipping and Export Controls:** Significant gaps exist in the regime governing shipping and export controls. For example, NIH shipping regulations currently treat a self-propagating gene drive organism no differently than a recombinant organism.¹⁴⁰ This gap may increase the risk of biosafety incidents as the network of groups exchanging materials grows nationally and internationally.
- **Dearth of Expertise and Support:** Many researchers and biosafety professionals that have roles in institutional oversight can lack expertise on new technologies, including gene drive experiments. Best practices literature also often lags behind technology development due to the increasing diversity of expertise needed to assess context-dependent risks, and the relative lack of support to develop these materials.

Options for Improving Oversight of Gene Drive Research and Development

- **Updating Standards for Research and Development:** Gene drive developers and sponsors could co-develop, update, and disseminate guidelines for gene drive research. For example, efforts like the Foundation for the NIH Gene Drive Research Forum can promote harmonization among an increasingly large and global group of funders. In conjunction, the NIH Guidelines could be updated to cover gene drive research with measures such as those proposed by leading gene drive researchers.¹⁴¹ The ASTMH could review and update the existing Arthropod Containment Guidelines to include gene drive arthropods. And the WHO-TDR could review, and where appropriate, update the “Guidance Framework for testing genetically modified mosquitoes.” As standards and guidance are developed, institutions could draw from and follow expert recommendations on best practices. Institutions could also offer gene drive biosafety training, such as those offered by ABSA, to Biosafety Officers and Institutional Biosafety Committee members.
- **Regulatory Requirements for Products:** The USDA, FDA, and EPA could require that any products that utilize gene drive technology under their jurisdiction be developed in accordance with any prospective research guidelines, even if the developer would normally be exempt from compliance with these rules (e.g. has not received public funding).
- **Applied Biosafety and Best Practices Research:** Funding support for applied biosafety research and best practice identification could be expanded, support which would help achieve goal 2.4.1--to strengthen biosafety and biosecurity--of the recently-released National Biodefense Strategy.¹⁴² Such research could range from social scientific research on effective policy design and implementation designed to guide behaviors to technical research on molecular and physical containment, detection and response. Ideally such work could be coupled to and integrated with technology development to keep policy in lock-step with new capabilities.

- **Recognition for Safety and Security:** To support researchers in recognizing risks and developing best practices, professional societies, such as the American Association for the Advancement of Science (AAAS), could confer named awards for excellence in biosafety and biosecurity research. Journals could include descriptions of biosafety innovations within individual manuscripts or special issues. Training programs in universities could also prioritize exposure to safety and regulatory research and highlight individuals that have played an active role in spotting gaps and updating policies.
- **Alert Systems:** Research institutions should develop systems to report both accidents and near-misses to ensure rapid responses and information are fed into networks that adapt policies and practices.

Context and Background: Oversight of Gene Drives and Emerging Biotechnologies

Oversight of gene drive research includes numerous parties. For federally funded research, oversight falls under the purview of the NIH.

NIH Guidelines and Institutional Biosafety Committees

The NIH Guidelines govern the safety of certain types of experiments with different degrees of oversight depending on the experiment type. Compliance with the NIH Guidelines is required for institutions that receive funding from NIH. The NIH Guidelines are written by the Recombinant DNA Advisory Committee (RAC). Institutional Biosafety Committees are the first line of review for research with recombinant and synthetic nucleic acids. All NIH-funded institutions are required to have an IBC composed of at least five members who have expertise in the fields of recombinant and synthetic DNA. The NIH guidelines contain a mechanism for individuals, institutions, and corporations to engage in voluntary compliance with the guidelines by forming IBCs, seeking certification of host-vector systems, and seeking approval or exemption for experiments that potentially fall under the purview of the guidelines.

Institutions that engage in large-scale experimentation with recombinant or synthetic organisms or operate BSL-3 or BSL-4 laboratories must have a Biosafety Officer (BSO), who is responsible for advising PIs and IBCs on safety procedures. The IBCs examine research protocols, expertise, potential hazard and containment plans. IBCs are required to register with the NIH Office of Biotechnology Activities (OBA), publish the minutes of their meetings, and submit annual reports to OBA. OBA provides resources and training on the role and responsibility of IBCs. Over time, IBCs have replaced the RAC as the primary entity overseeing rDNA research experiments.

The NIH often lacks insight into the performance of IBCs as uncovered by several studies that found that institutions either lacked IBCs, or the IBCs never met, or did not review specific proposals according to the NIH Guidelines.¹⁴³ Another longitudinal study found improved compliance rates among IBCs due to greater outreach by NIH and adverse media attention.¹⁴⁴ Given how novel gene drive technology is and how quickly the research is developing, many IBCs may not have the expertise or resources to effectively assess the biosafety of gene drive research.

The NIH Guidelines specify reporting requirements for significant problems, violations, and research-related accidents and illnesses. Non-compliance with the NIH Guidelines can lead to the loss of NIH funding. Although NIH has the power to terminate funding for violation of the Guidelines, it has never done so. Since the NIH is not a regulatory body it does not have the authority to conduct inspections, although it can and has conducted site visits.

A key weakness of biosafety oversight is that it is completely voluntary for institutions that do not receive NIH funding, such as pharmaceutical and biotech companies. Likewise, there is no outside

oversight of the safety of research conducted with naturally occurring pathogens that are not Select Agents or modified with recombinant or synthetic nucleic acids.

Context and Background: Best Practices Guidance

Best practices guidance literature helps communicate standards and procedures that, while not binding, gives practitioners a critical place to start in safeguarding biosafety. Given this importance, guidance literature must be regularly updated by various stakeholders who differ in expertise, mandate, and ability to communicate explanations to a wide variety of audiences. Authors often range from loosely organized peer scientists to professional organizations to international organizations.

Researchers

There is clearly a need for a bottom-up approach in which concerned researchers, who identify a critical need where best practices are not established or current literature is out of date, are enabled to take it upon themselves to develop and disseminate the best practices. For example, in 2015, a large number of scientists identified gaps in existing biosafety practices for gene drive experiments and published their own strategies to safeguard gene drive research.¹⁴⁵ This is a promising option as conscientious scientists are well-positioned to identify these needs through their own research experience and expertise. Nevertheless, many scientists lack the knowledge, skills, or resources required to ensure up-to-date and effective best practices, and even the most informed scientists may make mistakes. In other cases, given that compliance is voluntary, some researchers may choose to simply ignore sensible safeguards.¹⁴⁶

Professional Societies

Professional societies also provide biosafety guidance literature. For example, the American Society of Tropical Medicine and Hygiene publishes the Arthropod Containment Guidelines, which are widely used as guidance for arthropod containment. Nevertheless, the current ASTMH guidelines do not address gene drives.¹⁴⁷ Given the absence of federal guidelines, the American Biological Safety Association--which promotes biosafety in practice and as a discipline--offers training and courses on gene drive research to biosafety officers, and a framework for risk assessment and management of gene drive technology. Professional societies play a critical role in developing and disseminating best practices guidance.

The World Health Organization

International organizations (IOs) also play an important part in developing best practices guidance. But not unlike other actors who develop guidance, IOs may have difficulty keeping pace with technological developments. For example, the World Health Organization-Special Programme for Research and Training in Tropical Diseases (WHO-TDR) has developed a relatively comprehensive body of guidance literature on the field testing of genetically modified mosquitoes. The 2014 *Guidance Framework for testing genetically modified mosquitoes* addresses gene drive technology, but new CRISPR-based drives have since been developed. In fact, recommendations from the 2016 meeting of the WHO's Vector Control Advisory Group (VCAG), which advises on new vector controls designed to address vector-borne diseases, drew from the WHO-TDR guidance. The latter guidance does not address more recent forms of the technology, making their use as a resource by VCAG potentially problematic.¹⁴⁸

Scenario: Weaponized Bio-Narrative

This scenario illuminates how sowing doubt and fear about genome editing technologies can be used by actors to cause economic harm even if the imagined effects are not fully realized. The scenario revolves around an intentional release of a gene drive organism.

Simone Stephenson, an assistant professor at Woodward University in Pennsylvania, was motivated to become a research scientist because of her commitment to public health and the environment. She believes that gene drive research can address some of the most pressing health and environmental issues we face now and in the future. Dr. Stephenson's lab focuses on the mosquito species *Anopheles gambiae*, which is a major malaria vector in sub-Saharan Africa, and is an active area of gene drive research seeking to prevent malaria by suppressing vector populations.¹⁴⁹

Many environmental and anti-technology groups oppose the idea of editing the genomes of wild populations. Of particular concern to them is the potential impact that gene drives could have on **keystone species**, species on which an ecosystem largely depends, and whose alteration could disrupt the ecosystem.¹⁵⁰ While numerous ecological studies have determined that *Anopheles gambiae* is not a keystone species, nor thought to be important for the life cycle of any other species, a group called Natural World believes that the successful use of gene drive against malaria will create a slippery slope leading to the widespread use of this technology to target other species for extinction. A member of the group in Simone's social circle steals her access card at a party, which they use to break into Simone's laboratory and release numerous gene drive mosquitoes into the wild. The release is filmed and uploaded online.

The Natural World activists, which include some scientists among their ranks, know that the tropical *Anopheles gambiae* mosquitoes are highly unlikely to survive in Pennsylvania's late autumn climate. They believe that this relatively innocuous release will raise critical awareness of the longer-term risks they believe that gene drive research could present. A local journalist quickly learns of the release and writes an article in the city's major newspaper. The article is generally accurate, indicating the low probability of the altered mosquitoes' survival. National press outlets pick up the story, and most indicate that the risk of harm is low. Numerous Russian state-funded news outlets, however, use the story to highlight the "risks" of genetically modified organisms (GMOs) to human health and the environment, the role of greedy corporations and unaccountable philanthropies in funding GMO research, and the lack of effective government oversight.¹⁵¹ Because the mosquitoes have been genetically modified, these same news outlets link these "risks" to the mosquitoes' release. Several accounts on social media platforms pick up these themes.

As Natural World hoped, much of this reporting erroneously states that the release poses a threat to Pennsylvania's Little Brown Myotis (aka Little Brown Bat), which feeds on mosquitoes and is a keystone species in the state.¹⁵² Additional false narratives focus on the risk of the mosquitoes contaminating food crops with genetically engineered organisms. This narrative moves from fringe social media accounts to more mainstream science skeptics. An independent review indicates that

many of these accounts have links to troll factories overseas. Other environmental activist groups begin taking up the narrative, followed by affinity groups in countries that are U.S. trading partners and have strict laws governing the import of GMOs. The impact of public perception of gene drive and broader biotechnology research is not yet clear, nor are the economic impacts. Lost in the buzz surrounding the story is that the goal of Dr. Stephenson's research is to eradicate malaria, which kills over 400,000 people a year, primarily in Africa.

Takeaways

- **Emerging Uncertainties:** A rapidly changing field of research and development like genome editing and gene drive engineering is characterized by a high degree of uncertainty about uses, effects, and safety. Reducing these uncertainties requires additional research.
- **Risky Communications:** When public dialogue about these new technologies occurs in an already polarized and politicized background, lack of clear information, combined with the contested nature of any new potentially "risky" technologies, can lead to highly polarizing communications that feed into narratives of fear and doubt.
- **Cascading Impacts:** Even if the effects are not realized at a physical level, the psychological effects could lead to large and long-term impacts on research and the economy. For example, domestic and international laws and institutions could be used to erect trade barriers in the event of an accidental release.
- **Outside Interventions:** While there is a focus on ensuring safe practices by researchers, there are a variety of actors who have different motives and incentives to directly intervene in laboratory research and field trials, as well as to leverage incidents to spread misinformation.

Options to Mitigate the Threat of Weaponized Bio-Narratives

- **Communications Strategies:** Research institutions, funders, and professional associations could develop communications strategies for incidents and anomalies that recognize the uncertainties in research. Proactive engagement of potentially affected populations and broader publics, well before any incidents occur, could help dispel misinformation and create trusted channels of communication should concerns arise. Planning and training for effective communication may take many forms, but could involve professional societies developing "bio-bootcamps" to educate members of the media and scientists on biosafety and biosecurity issues. Professional societies, such as AAAS, could also offer science communication and security fellowship programs that enable wider networks of trusted communicators.
- **Countering Misinformation:** Media platforms and communications research centers could examine strategies to identify and manage misinformation specific to security and emerging technologies in the life sciences.
- **Biosecurity Awareness:** Researchers and policymakers should be aware that there is a risk of outside interference in laboratory development and trials and, to the extent practicable, have a communications strategy in the event such interference that arises.
- **Defense Technologies:** Further developing surveillance and forensics capacity could increase the chance of detecting a release, ensuring public safety, and attributing releases to bad actors. Because there is the chance that some released organisms will pose a risk, the U.S. government could continue to develop prophylactic and therapeutic treatments against

genome editors, and remedial strategies designed to restore systems to functional and genetic baseline states.

- **Avoiding Mutually Assured Misinterpretation:** States that pursue the development of defense technologies should endeavor to signal to allies and adversaries that such technologies are defensive in nature and in keeping with the letter and the spirit of applicable treaty obligations.

Context and Background: Life Sciences Media and Impacted Communities

The prevalence of fake news and information warfare could be used to push false narratives about research in the life sciences.

Lack of informed public knowledge about genome editing, and disagreements about its legitimate uses may perpetuate and fuel misconceptions about research, applications, and risks of genetic technologies. Less than 20% of Americans report that they are knowledgeable about GMOs.¹⁵³ Recent public opinion data indicates that approximately 70% of Americans approve of genetic engineering of mosquitoes to prevent vector-borne illnesses, but are opposed to other uses of genome editing technology in animals.¹⁵⁴ Recognizing an area of technology that was already a subject of debate, Russian state-funded English language news outlets have released and promulgated false information about the safety of GMOs. It is plausible that similar information warfare tactics could be used to exploit Americans' lack of knowledge and opposition to particular forms of genome editing, especially in new and contested areas such as gene drive. Even if an accidental release or field trial poses little to no physical or ecological risk, such misconceptions could badly damage public trust in biotechnology and its governance, and negatively impact gene drive research. At the international level, it is possible that a State could erect trade barriers under the World Trade Organization's sanitary and phytosanitary measures, which "protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms."¹⁵⁵ Such barriers could be erected in order to gain political or economic advantage even if the risk is unwarranted.¹⁵⁶

Context and Background: Defense Technologies

Attributing and mitigating misuses of technologies will require new innovations.

The physical and psychological damage from release of a genetically engineered organisms or genetic constructs will dependent in part on how quickly an event can be detected, its source identified, its effects characterized, and any harmful effects neutralized. As the anthrax attacks of 2001 demonstrated, a relatively minor incident compared to what was possible, when combined with misleading messaging and an already tense climate, can fuel a cascade of attention that can dramatically reshape a security and governance regime towards an assumed threat before that threat can be confirmed. With more rapid attribution and detection of the scale of risk, then resources and attention can be more efficiently and strategically deployed to mitigate the threat.

Detecting and responding to an increasingly diverse and complex landscape of threats beyond traditional agents and actors is a formidable technical challenge. Underlying the ability to implement, for example, a potential policy to screen orders for new potentially dangerous agents relies on the

science to predict and identify these agents. In this way, the challenge of implementing security measures often mirrors the foundational science and engineering challenges.

Recognizing this challenge, several government funders have developed programs to further develop surveillance and forensics capacities, prophylactic and therapeutic treatments, and remedial strategies to restore systems to functional and genetic baseline states. **DARPA** and **IARPA** have notable biosecurity initiatives that examine different elements of these challenges. DARPA has launched several research programs under its biotechnology office that are designed to develop versatile platforms that can be customized to address novel threats and be scaled up and distributed quickly. Of particular note is DARPA's Safe Genes program, which seeks to develop technologies to protect, detect, and respond to the accidental or intentional misuse of genome editing technologies alongside technical development. Meanwhile, IARPA has advanced new programs to develop biosecurity tools: The Functional Genomic and Computational Assessment of Threats (Fun GCAT) program seeks to develop functional annotation of genes of concerns, and the Finding Engineering-Linked Indicators (FELIX) program seeks to develop new experimental and computational tools to detect engineered biological systems.

It remains an open, and contested, question as to who should be in the business of developing these technological applications. The wide number of applications means biotechnology cuts across nearly every aspect of the defense mission space - from medical applications, to new sensors, to new materials. Yet these programs have come under criticism for their militarization of biology and for their potential to develop technologies that could have offensive applications.¹⁵⁷ With DARPA being a significant funder in particular areas of biotechnology, these concerns end up being even more pronounced. Clearly communicating the defensive nature of programs, and signaling their accord with treaty obligations, will be increasingly important in ensuring that these programs do not lead to mutually assured misinterpretation of efforts. In addition to programs that develop new biodefense technologies, such programs can also serve to introduce practitioners to the security mission space. Indeed, programs such as DARPA's Young Faculty Award program is specifically designed to orient emerging leaders to national security needs and communities.

Summary

Designing effective safety and security governance measures for a generative technology, such as genome editing, is challenging. Despite barriers to use, the relative accessibility of the technology, in terms of acquiring the necessary material and skills to use it, makes it attractive to a wide range of actors with diverse motives and objectives. The versatility of the technology enables these actors to develop a variety of products in a number of disparate application areas.

The current system for governing the safety and security dimensions of biotechnology is fragmented and based on a patchwork of laws, regulations, policies, and voluntary measures at the national and international levels. At a minimum, existing governance measures need to be updated to consider the growing capabilities offered by genome editing in the fields of agriculture, biomedical research, human health, and the broader industrial bioeconomy. While sometimes these are specific to genome editing, in many cases they address broader challenges associated with a suite of technologies that enable us to explore and exploit biological systems with increasing ease. In some cases, governance updates will be minor and incremental. In other cases, governance measures may have to be radically revised in order to achieve the objectives they were designed for. There may also be cases where brand-new initiatives at the national or international level are needed to fill a critical gap in the governance architecture.

KEY TRENDS, TAKEAWAYS, AND CONCLUSION

Genome editing has the potential to improve the human condition.

Genome editing is a powerful technology that promises to enable a wide range of tools and applications across a number of domains. Despite its great potential, technical and social barriers to both its beneficial use and misuse remain. Realizing the promise of this enabling technology over the long-term will depend on society's ability to facilitate beneficial research and development and prevent and, if necessary mitigate, the potential risks posed by the technology.

Indicators point to a rapid acceleration of technical capability, economic investment, and product development in genome editing that is having significant impact on science and the economy. The market for genome editing is expected to exceed \$3.5 billion by 2019, but a security incident, biosafety lapse, reckless conduct, or significant regulatory uncertainty could hamper this growth. As we become ever more reliant on the bio-economy, which includes all facets of agriculture, health, industrial biotechnology, and living environmental resources, the relevance of biosecurity and economic security to the human condition is critical, as is the ability for game-changing technologies like genome editing to disrupt this security.

Genome editing is disruptive to the biosecurity landscape.

Genome editing presents a significant and urgent challenge for contemporary biosafety and biosecurity regimes, which are focused on outdated threat vectors, and 20th century conceptions of biological risks. The growth of the biological attack surface has expanded dramatically due to the open source nature of the life sciences research enterprise, the globalization of its innovators and users, and the increasing integration of biotechnology into the economy. Developments in genome editing have compounded the complexity of this landscape by creating new potential attack vectors and the means for rapidly identifying additional ones. Indeed, many of these new attack vectors do not involve actual pathogens, but instead involve genetic constructs and associated means of delivery. Since the current biodefense paradigm is oriented around developing defenses against a short list of known pathogens, and most defenses are agent-specific, these new attack vectors have the potential to circumvent current defenses, and raise new attribution challenges. Since 2001, the United States has invested heavily in microbial forensics, but again, these capabilities are geared towards the analysis and characterization of traditional biothreat pathogens. Although there remain significant barriers to misuse of genome editing in the near-term for states, in the medium-term for skilled groups, and in the longer-term for skilled individuals, the emergence of genome editing, and CRISPR in particular, poses a new set of challenges to biosafety, biodefense, and biosecurity.

The rapid adoption of genome editing by wide swathes of the life sciences community has created a large and heterogeneous population of users. When combined with the broadened range of potential risks, the growing commercialization of the technology for research, medical, public health, and

agricultural applications, as well as unforeseen use cases that are yet to emerge, the security landscape may be further disrupted, and the attack space likely to grow.

CRISPR illuminates broader trends and challenges in an evolving security landscape.

CRISPR is unique in that the virtuous cycle enabled by scientific, legal, and organizational factors have contributed to making it the *de facto* genome editing tool of choice. Consequently, the multiplicity of techniques and applications for which CRISPR is being used, and the wide array of actors involved, means that the potential risks it poses are multidimensional and stretch across such domains as biosecurity, biosafety, dual-use research, and reckless conduct. Each of these risks differs in important ways in terms of likelihood, urgency, scope and scale of consequences, and relevant stakeholders.

But neither CRISPR, nor genome editing more generally, can be viewed in isolation. CRISPR is part of a suite of enabling technologies, alongside other basic functions like the ability to synthesize DNA, that are being leveraged to explore and exploit biomolecular functions. Moreover, other emerging technologies being applied to the life sciences, such as artificial intelligence and robotic automation, have the potential to enable new capabilities that can radically alter the biosecurity landscape. Scientific, technological, economic, and social trends are increasing the range of potential biological hazards, diversifying the sources of these hazards, multiplying the routes of exposure, expanding the populations that may be exposed, and increasing these populations' level of susceptibility. An approach to biosecurity that accounts for these trends, and encompasses risks posed by deliberate, accidental, and reckless misuse, can help navigate the complex and evolving security landscape. This approach can illustrate the array of potential risks posed by misuse of emerging technologies and areas of commonality among the governance options for addressing them.

Take the technology seriously.

A thorough, informed, and accessible analysis of a given technology and its social context is crucial to considering the impact that it may have on the security landscape. This report, and the broader *Editing Biosecurity* study, by its nature have emphasized this need. Absent such detailed analyses, actors may issue pronouncements of risk and impact that are based on unfounded assumptions, which can strain credibility, putting stakeholders in a poor position to assess the veracity of these claims. Perhaps more worrying is the possibility that those issuing these pronouncements are high-level government officials who have the power to influence and command policies and resources that would be better focused elsewhere, or that these statements have unintended consequences. Often the key actors best equipped to provide analyses of what is possible and plausible are those who work closely with the technology. In addition, those closest to the science and the variety of applications in different domains can help capture key trends. Engaging technologists in sustained dialogue with social scientists and policy makers can illuminate the security-related aspects of these trends that may be less salient at the ground level, while also equipping technologists to appreciate and help undertake governance actions.

Key stakeholders must be engaged.

Stakeholders in the genome editing field encompass a more diverse array of actors than those involved in previous biosecurity discussions. Consequently, the engagement of new communities of actors is required, particularly those who can play important roles in preventing or mitigating misuse. As genome editing technology becomes more accessible, there will be increasingly important governance roles for technology developers, including organizations providing access to critical information and materials. The dynamic security landscape and the diversity of stakeholders also means that governance measures for genome editing technology cannot take a one-size-fits-all approach. Instead, governance measures need to be tailored depending on the application in question, the nature of the relevant stakeholders, and the type of misuse being addressed. Implementing the policy options discussed in this report will require the buy-in and active participation from multiple groups of stakeholders. These stakeholders range from international organizations to government agencies to universities, companies, and scientists. Developing a shared understanding of the range of potential risks, even if it is not possible to reach consensus on the urgency and severity of each risk, would provide a foundation for dialogue that is key to successful collaboration.

The diverse and cross-cutting collection of recommendations offered by this report is a recognition of the need for an expansive and adaptive approach to governing fast-moving, widely-used, and rapidly-diffusing technologies. This need will likely continue in the area of biosecurity as other technologies emerge, and genome editing is a bellwether for trends in biosecurity and emerging technologies in the life sciences.

Applied research is needed to create and implement innovative and effective policies.

Applied governance research is necessary to continue the process of modifying existing governance measures, and developing new ones, as more genome editing technologies and applications are developed, new stakeholders emerge, and new pathways for misuse are identified. More focus and funding could be put towards enabling this type of work across government and non-governmental organizations, including universities, companies, and research consortia. Such research could range from social scientific research on effective policy design and implementation designed to guide behaviors, to the development of best practices for nurturing cultures of safety and responsibility in academic, corporate, and community labs to analyses of the impact of online multimedia resources on the transmission of tacit knowledge. This research could also include programs that facilitate the design, building, and testing of governance measures, including developing technical innovations that address a governance need. Such measures can be implemented on a temporary or small-scale in order to collect better data necessary for larger-scale initiatives, and to adapt and update governance measures as necessary and appropriate. This research can serve as a building block for filling future governance gaps in the area of biosecurity.

The design of research programs and the composition of research teams must also account for the trend toward a more diverse range of actors in the life science and security enterprise. Strong leadership and large-scale institutional commitments will be necessary in order to identify the key stakeholders and actors, facilitate relationships among the relevant parties, and put them into productive engagement.

Conclusion: A Path Forward

A Strategy of Collaboration: Working Toward and Hoping for the Best

The dominant theories of how public policy is made can be likened to the theory of punctuated equilibrium from evolutionary biology: policies, like species, remain static or undergo only incremental changes until an exogenous event creates the conditions necessary for a dramatic change.¹⁵⁸ This reactive model of policy-making, however, is widely viewed as being unsuited for an era of rapid technological change. There are no simple and easy solutions to the myriad safety and security challenges posed by genome editing in particular and advances in biotechnology more broadly. Indeed, the oversight of dual-use research has been described by one of the authors of this report as a “wicked problem,” which is characterized by multiple, overlapping subsets of problems and high levels of social complexity driven by the number and diversity of players involved in problem-solving.¹⁵⁹

The scientific community understandably prefers self-governance: to determine for themselves the best ways to balance safety, security, and the pursuit of science. Indeed, there are good examples of the biology community acting proactively to address concerns about safety and security. The 1975 Asilomar conference of molecular biologists led to the creation of the Recombinant Advisory Committee at NIH and the creation of Institutional Biosafety Committees at research institutions to ensure the safety of experiments with recombinant DNA. In the late 2000s, the DNA synthesis industry established standards for screening of customers and sequences to reduce the risk of the misuse of synthetic biology. Yet, self governance is only effective if the appropriate stakeholders are identified and engaged, and opposing viewpoints are aired and seriously considered.

One of the more effective, but difficult, strategies for coping with a wicked problem is for stakeholders to collaborate on designing policies that can be widely accepted and broadly adopted, even if they are not optimal from the perspective of any single stakeholder.¹⁶⁰ Successful collaboration is more likely to emerge if stakeholders engage in intensive dialogue as a means of building a shared understanding about the problem, a common language to discuss it, and a shared commitment to solving it. Dialogue is an integral part of the process of creating a shared vision among a diverse group of stakeholders, particularly when each stakeholder brings practice-based “local knowledge” to the table, which can be hard to share and difficult for other stakeholders with different identities to internalize. Collaboration can also be facilitated by the emergence of a “collaborative capacity builder,” an individual or organization whose role is to ensure the integration of knowledge among stakeholders as part of a long-term strategy to foster a collaborative environment for continuously addressing the issue.¹⁶¹

There are already some signs of this type of collaboration in the field of genome editing, but much more is needed. One leading example is the collaboration between the U.S. National Academies of Science and Medicine, the U.K. Royal Society, and the Chinese Academies of Science to convene a series of international summits that bring together a broad range of stakeholders to discuss the medical, social, and ethical aspects of human genome editing.¹⁶² Another promising example was an international workshop in 2017 devoted to biosecurity organized by the U.S. National Academies of Science, Engineering and Medicine, the European Academies Science Advisory Council, and the German National Academy of Sciences Leopoldina.¹⁶³ Such collaborations are encouraging, but

future meetings need to have security featured as a repeated, enduring, cross-cutting, and built-in theme. Without broadening the aperture, we will not get the full picture, and thereby hazard missing the full scope of the genome editing landscape.

Innovation as Security Strategy: Hedging Against the Worst

Given the overall trend towards a more diverse threat landscape, we need to reconsider how we conceive of and manage biosecurity. Advanced biotechnologies are developing rapidly and globally and therefore the capability to use them to cause harm will be readily available for a range of actors. Whether these technologies are handled responsibly or used for malicious purposes ultimately depends on the intent of the actor. Therefore, the United States and other countries need to be prepared to encounter and cope with a range of novel biological threats.

It is sobering that we face a future where we can mitigate but cannot prevent misuse; we therefore must use innovation as a security strategy.

We can envision innovation as a security strategy anchored by resilience. Resilience seeks to harness genome editing to strengthen defenses against current natural and human-made biological threats. But the larger attack surface created by genome editing will make it extremely difficult to predict what vectors and which vulnerabilities may be exploited to cause harm. To fully prepare for these uncertainties is an impossibility. Consequently, resilience also seeks to use genome editing to cope with the potential threats posed by the technology and recover should such threats be realized. Each of these components use genome editing in different ways but at their heart share the common goal of pushing advanced technologies to the next level to achieve revolutionary changes in capabilities.

It remains an open, and contested, question as to who should be in the business of developing these technological applications. It is in the clear interest of states to do so, and the U.S. has taken the lead. DARPA has launched several research programs that could be characterized as using the strategy of resilience. The overarching goal of such a resilience strategy is to develop versatile platforms that can be customized to deal with novel threats and be scaled up and distributed quickly. These programs have come under criticism for their militarization of biology and for their potential to develop technologies that could have offensive applications.¹⁶⁴ These concerns need to be taken seriously and addressed by any actors developing such technologies. The resilience strategy is rational if one thinks the spread of genome editing is inevitable and there exists credible evidence or belief that potential adversaries are, or may in the future, seek to exploit this technology for offensive purposes. The primary concern is that the technology that is developed could also be adapted for offensive use. If the threat is distant and diffuse or merely hypothetical, then such programs risk provoking the very arms race that is in everyone's interest to avoid. This is a classic security dilemma; what is rational may not be optimal.¹⁶⁵ States would do best to avoid entering into a regime of mutually assured mis-interpretation.

The genome editing field is arguably near an inflection point. While still a relatively new field in the annals of science, it has been six years since the publication of the seminal paper by Jennifer Doudna and Emmanuelle Charpentier that first identified the potential of CRISPR/Cas9 to make

precise edits to DNA, and the subsequent paper by Feng Zhang that demonstrated its use in eukaryotic cells. The technology has quickly diffused globally, companies have grown, and gene editing has started to enter public consciousness. During CRISPR's rise, discussions about the societal impact has focused primarily on the ethics of human germline editing and ecological implications of using gene drives to control mosquito populations, and to a lesser extent on the security implications of the technology. Because CRISPR has proven to be so versatile, it has unlocked a much broader array of capabilities that enable a wider range of actors to modify a diverse array of organisms in a multitude of ways. The path forward will require a pragmatic compromise. We must hope for the best and hedge against the worst. Simultaneously, increased collaboration between the science and policy communities is needed to better formulate and implement governance measures that will preserve the benefits of genome editing while providing safeguards against accidental, inadvertent, or deliberate misuse.

Finally, stakeholders must recognize that many of the issues identified here are not unique to genome editing. Instead, they are representative of broader systemic challenges created by advances in the life sciences and biotechnology; challenges that will only grow more complex over the long-term. Unless the process of modernizing existing governance measures to ensure the safe, secure, and responsible use of biology begins today, the scientific and policy communities will find it even more difficult to take effective action in the future.

Glossary

Allele - a variant form of a gene.

Attack Surface - a term used by the cybersecurity community to describe the number, accessibility, and severity of vulnerabilities in information technology systems that could be exploited to cause harm, either deliberately or accidentally.

Binding domain - a protein element that binds to a particular molecule.

Bioinformatics - interdisciplinary field that deploys computational approaches to understand biology.

Biological Weapons Convention (BWC) - the 1972 treaty banning the development, production, and acquisition of biological weapons.

Biosecurity - measures to prevent, prepare for, and respond to risks of deliberate, accidental, inadvertent, and reckless misuse of biology and biotechnology.

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats; a defense mechanism found in bacteria that has been adapted to make precise cuts in DNA.

Defense Advanced Research Projects Agency (DARPA) - a research organization within the U.S. Department of Defense with the goal of developing breakthrough technologies for national security.

Delivery - the process by which a molecule is introduced to a particular cell or organism.

Delivery vector - the physical format through which a molecule is delivered to a cell or organism.

DNA synthesis firm - a company that specializes in the production of synthetic DNA for use by scientific or commercial customers.

Double strand break (DSB) - the severing of both strands in the double helix of DNA which can trigger a natural DNA repair method or create an opportunity to insert new DNA.

Eukaryotes - an organism consisting of a cell or cells in which the genetic material is DNA in the form of chromosomes contained within a distinct nucleus. Eukaryotes include all living organisms other than bacteria and archaea, which are known as prokaryotes.

Gene drive - a genome editing technology enabled by CRISPR that can propagate a particular suite of genes across successive generations of descendants even if the genes do not necessarily confer a fitness advantage.

Genetic transformation - the process by which the genetic makeup of a cell is altered by taking up DNA from the environment.

Generative technology - a platform technology or technological ecosystem that allows a diverse range of users to create, share, and modify new applications in a decentralized manner.

Genome - the complete set of genetic information found in an organism's chromosomes.

Genomic DNA - most organisms have the same genomic DNA in each of their cells, and a complete genome is unique to an individual other than in the case of clones (identical twins or cuttings).

Genome editing - a type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome of a living organism in specific locations.

Genome Editing Vector (GEV) - a delivery vector used to deliver essential components of a genome editing tool into a cell.

Genome editing reagents - a general term used herein to describe the wetware materials required for a genome editing procedure.

Genotype - the set of genes responsible for a particular trait.

Germline editing - the process by which the genome of an individual is edited in such a way that the change is heritable.

Guide / guide RNA - a nucleic acid based binding domain used in CRISPR genome editing.

High-throughput screening (HTS) - a capability to conduct many millions of experiments simultaneously that is useful for screening large populations of modified cells to discover complex multigenic phenotypes for later exploitation.

Intelligence Advanced Research Projects Activity (IARPA) - a U.S. organization, within the Office of the Director of National Intelligence, that is responsible for leading research to overcome challenges relevant to the U.S. Intelligence Community.

Immunizing reversal drive - a type of gene drive that overwrites changes made by an unwanted gene drive and immunizes unaffected populations by recoding the DNA sequence targeted by the unwanted gene drive without changing the organism's phenotype.

In vitro fertilization (IVF)- a type of assisted reproductive technology where an egg is fertilized by sperm in a lab to create an embryo which is then transferred to the recipient.

International Gene Synthesis Consortium (IGSC) - an industry-led group of DNA synthesis companies and organizations formed to design and apply a common protocol to screen the sequences of synthetic gene orders and the customers who place them.

Keystone species - species on which an ecosystem largely depends, and whose alteration could disrupt the ecosystem.

Microbiome - the microbiome is the collection of microorganisms that occupy the same ecological niche in a host or in the environment.

Molecular cloning - is a set of methods in molecular biology that are used to create recombinant DNA molecules.

Mosaic - a population of cells or an organism with a variable genotype.

Nuclease - an enzyme known to cleave nucleic acid sequences.

Off-target effects - refers to nonspecific and unintended genetic modifications, such as point mutations, deletions, and insertions, that can arise through the use of genome editing techniques such as CRISPR, TALENs, and ZFNs.

Oligonucleotide - a short string of nucleic acids, sometimes referred to as an oligo.

Payload - the entire set of materials or reagents or GEVs and additional components delivered to a cell during a genome editing procedure.

Phenotype - the physical expression or characteristics derived from a genotype.

Plasmid - circular non-genomic DNA vectors that may be used to transfer extrachromosomal DNA between organisms, or otherwise used as a GEV.

Prokaryotes - microscopic single-celled organisms, including bacteria and archaea, that have neither a distinct nucleus with a membrane nor other specialized organelles.

PAM (Protospacer Adjacent Motif) - a recognition site for some RGEN.

Reference genome - a representative approximation of an organism's DNA, used to understand an average genome for a particular species.

RGEN (RNA-guided endonuclease) - a nuclease that is guided to its target by a programmable element, such as a guide RNA.

Safe Genes Program - Safe Genes is a Defense Advanced Research Projects Agency program that supports force protection and military health and readiness by protecting Service members from accidental or intentional misuse of genome editing technologies.

Somatic genome editing - the process by which the genome of an individual is edited in such a way that the change is not heritable.

TALEN (Transcription activator-like effector nuclease) - a genome editing technique that utilizes a pair of Transcription activator-like proteins coupled with a pair of Fok1 nucleases.

ZFNs (Zinc-finger nucleases) - a genome editing technique that utilizes a pair of binding domains built proteins called zinc fingers to guide a pair of Fok1 nucleases.

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Prior to arriving at George Mason, Dr. Koblentz was a visiting assistant professor in the School of Foreign Service and Department of Government at Georgetown University. He has also worked for the Executive Session on Domestic Preparedness at the John F. Kennedy School of Government at Harvard University and the Nuclear Non-Proliferation Project at the Carnegie Endowment for International Peace. Dr. Koblentz is the author of *Strategic Stability in the Second Nuclear Age* (Council on Foreign Relations, 2014) and *Living Weapons: Biological Warfare and International Security* (Cornell University Press, 2009) and co-author of *Tracking Nuclear Proliferation: A Guide in Maps and Charts* (Carnegie Endowment for International Peace, 1998). His research and teaching focus on international security and weapons of mass destruction. He received a PhD in political

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Dr. Megan J. Palmer is a Senior Research Scholar at the Center for International Security and Cooperation (CISAC) at Stanford University. She leads a research program on the governance of biotechnology development with a focus on how security is conceived and managed. Her current projects focus on assessing strategies for governing dual use research, analyzing the international diffusion of biosafety and biosecurity norms and practices, and the understanding the security implications of alternative technology design decisions. Dr. Palmer has also created and led many programs aimed promoting the responsible development of biotechnology. She also leads programs in responsible innovation for the international Genetically Engineered Machine (iGEM) competition, which last year involved over 5000 students in 340 teams from 48 countries. She also founded and serves as Executive Director of the Synthetic Biology Leadership Excellence Accelerator Program (LEAP), an international fellowship program in biotechnology leadership. Previously, Dr. Palmer spent 5 years directing the policy-related research program for the Synthetic Biology Engineering Research Center (Synberc), a multi-university research center in synthetic biology. She has also held positions as the William J. Perry Fellow in International Security at CISAC, a research scientist at the California Center for Quantitative Bioscience at the University of California Berkeley and a postdoctoral scholar in the Bioengineering Department at Stanford University. Dr. Palmer holds a Ph.D. in Biological Engineering from MIT and a B.Sc.E. in Engineering Chemistry from Queen's University, Canada.

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Relman was an early pioneer in the modern study of the human indigenous microbiota (microbiome). A landmark paper in 2005 was one of the first to describe the human gut microbiota with molecular methods. Most recently, his work has focused on human microbial community assembly, and community stability and resilience. Principles of disturbance and landscape ecology are tested in clinical studies of the human microbiome. Previous work included the development of methods for pathogen discovery, and the identification of several historically important and novel microbial disease agents. One of those papers was selected as “one of the 50 most important publications of the past century” by the American Society for Microbiology.

Among policy-relevant activities in health and biological security, Relman served as vice-chair of the National Research Council Committee that reviewed the science performed for the FBI 2001 Anthrax Letters investigation, chair of the Forum on Microbial Threats (2007-2017), a member of the Committee on Science, Technology & Law (2012-2015), and is currently a member of the Intelligence Community Studies Board (2016-), all at the U.S. National Academies of Science. He was a founding member of the National Science Advisory Board on Biosecurity (2005-2014), a member of the Working Group on Biodefense for the President’s Council of Advisors on Science and Technology (The White House) (2016), and served as President of the Infectious Diseases Society of America (2012-2013). He is currently chair of the Board of Scientific Counselors at NCBI/NIH. He was a recipient of NIH Pioneer and Transformative Research Awards, and was elected to the National Academy of Medicine in 2011.

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Disclosures

Gregory D. Koblentz has agreed to serve as a volunteer advisor to DARPA's PREPARE program on the ethical, legal, and social implications of using genome editing technology to develop defenses against chemical, biological, and radiological hazards.

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