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Genome editing and biosecurity

BACKGROUND PAPER

September 2017

Introduction

In October 2017 leading professional scientific bodies are convening a meeting to assess the security implications of genome editing technologies.¹ Participants will consider the security implications of the latest advances in genome editing and current and potential applications relating to a wide range of organisms such as microbes, plants, animals and humans. The meeting will address the debates over their potential risks and misuse - exploring near- middle- and long-term security concerns and consider technical, operational, regulatory and governance strategies that may prevent or mitigate them.

The October 2017 workshop builds upon a cadre of earlier work looking at the technical and socio-political implications of gene editing technologies, in particular those associated with the use of these technologies as research tools, for clinical therapy in a targeted individual (somatic gene editing), and for clinical application in inherited traits (germline interventions). The first part of this background paper introduces many relevant reports and resources produced in recent years.

Potential security implications for genome editing technologies were highlighted in February 2016 when the then-Director of National Intelligence in the United States labelled these technologies as a national security threat. The second part of this document summarizes recent discussions as to possible security implications. It draws upon materials published in top-tier technical journals, science bodies, meeting reports, and reputable general science publications over the last two years.

One specific application of gene editing technology, through gene drives, has received particular attention. They potentially place a global impact into the hands of small groups. The third part of this study provides an overview of past discussions on the possible security implications of gene drives.

Acknowledgment

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¹ Genome editing is sometimes referred to as gene editing, but that the former is used throughout this document because it is generally felt to be more accurate, and is used in many reports and papers on the topic.



Part I: Policies, positions and guidance from the scientific community

The scientific community² has produced a wide range of policies, positions and guidance relevant to genome editing technologies.³ They include work in two areas: (a) reports focused directly on genome editing technologies; and (b) broader consideration of the implications of developments in the life sciences and biotechnology.

Reports that focused directly on genome editing include:⁴

1. Federation of European Academies of Medicine. [Human Genome Editing in the EU](#) (2016)
2. European Academies Science Advisory Council. [Genome editing: scientific opportunities, public interests and policy options in the European Union](#) (2017)
3. Australian Academy of Science. [Synthetic gene drives in Australia: implications of emerging technologies](#) (2017)
4. National Academy of Sciences Leopoldina. [Academies issue statement on progress in molecular breeding and on the possible national ban on cultivation of genetically modified plants](#) (2015)
5. National Academy of Sciences Leopoldina, the German National Academy of Science and Engineering, the Union of German Academies of Sciences and Humanities, and the German Research Foundation. [The opportunities and limits of genome editing](#) (2015)
6. National Academy of Sciences Leopoldina. [Ethical and legal assessment of genome editing in research on human cells](#) (2017)
7. Royal Netherlands Academy of Arts and Sciences. [Genome editing position paper](#) (2016)
8. Royal Society of New Zealand. Gene Editing [Evidence Update](#) and [Expert Advice paper](#) (2016)
9. Academy of Science of South Africa and Department of Science and Technology of South Africa. [The regulatory implications of new breeding techniques](#) (2017)
10. UK House of Lords Science and Technology Select Committee. [Genetically Modified Insects](#) (2015)
11. US National Academies. [Genetically Engineered Crops: Experiences and Prospects](#) (2016)
12. US National Academies. [Gene Drives on the Horizon](#) (2016)
13. US National Academies. [Human Genome Editing: Science, Ethics and Governance](#) (2017)

Reports that addressed broader implications of developments in the life science and biotechnology include:

14. IAP. [Responsible Conduct in the Global Research Enterprise](#) (2012)
15. IAP. [The Biological and Toxin Weapons Convention: Implications of advances in science and technology](#) (2015)

2 The scientific community in this context includes, in addition to life scientists and biotechnologists, ethicists, legal experts, clinicians, and other relevant disciplines.

3 Given the overlapping content of many of these reports, throughout this report indicative references have been provided. Many of the other non-referenced reports make similar points.

4 Throughout the body of this report, numbers in parentheses reference documents on this list. Other references are provided via links in the footnotes.



16. Leopoldina. [Scientific Freedom and Scientific Responsibility: Recommendations for Handling Security-Relevant Research](#) (2014)
17. Leopoldina and German Research Foundation. [Joint Committee on the Handling of Security-Relevant Research](#) (2016)
18. Academy of Science of South Africa. [The state of biosafety and biosecurity in South Africa](#) (2015)
19. Swiss Academies of Arts and Sciences. [Misuse potential and biosecurity in life sciences research](#) (2017)
20. US National Academies. [Understanding Biosecurity: Protecting Against the Misuse of Science in Today's World](#) (2010)
21. US National Academies. [Preparing for the Future Products of Biotechnology](#) (2017)
22. US National Academies. [Proposed Framework for Identifying Potential Biodefense Vulnerabilities Posed by Synthetic Biology: Interim Report](#) (2017)
23. US National Academies. [Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies](#) (2017)

Genome editing

Many of the reports that focus on genome editing provide overviews of what it is and what tools are involved. They largely focus on four types of method: meganucleases (MNs), Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs) and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) guide RNAs used with Cas9 or related nucleases.⁵ They also address key international meetings on the subject, including the 2015 [International Summit on Human Gene Editing](#) and the 2016 [Workshop on Human Genome Editing in the EU](#).

Genome editing reports can be divided into those that look at its applications relevant to humans (1), and those that look at its applications for plant breeding (4).

Potential benefits of genome editing

Genome editing is a powerful technology. “Because of its general applicability (in microbes, and plant, animal and human cells) it has a very wide range of potential uses in tackling societal objectives” (4), including in: public health (1,2,5,7); developmental biology (1); plant and animal breeding in agriculture (1,2,4,7,8), including improving animal welfare or production traits (7,8); research models (2,8), including for human embryonic development (6), or the development of new animal models (7); xenotransplantation (1,2,7); the bioeconomy and biotechnology as a manufacturing platform (2,8); and perhaps even the creation of new pets, such as micropigs (8).

Potential risks of genome editing

As with other forms of life science research and biotechnology, there is a recognition that the risks associated with genome editing need to be assessed and managed through biosafety and biosecurity measures (7, 21).

There have also been concerns over the specificity and off-target effects of genome editing: could it have an impact on organisms if it alters genes to which the targeting was not intended, or could it alter

⁵ One notable difference between these methods is that those based on CRISPR are sometimes referred to as ‘RNA-guided genome editing’, as opposed to protein guided as in the case of MNs, ZFNs and TALENs.



the genome of a bone-fide target in undesirable ways? Progress has been made in developing tools to assess the specificity and possible off-target events of genome editing technologies, such as *in silico* prediction methods, and molecular-based methods, such as GUIDE-seq⁶ and Digenome-seq (11).

Genome editing enables genetic modification. Those with concerns over genetic modification have expressed similar concerns over genome editing (2):

Concerns have been expressed, by some non-governmental organisations (NGOs) for example, that genome editing is 'not natural', that there are too many gaps in our knowledge, that impacts are uncertain and may be inequitable, and that regulation cannot keep pace with the speed of technological innovation.

It has also been suggested that developments in genome editing technologies have complicated differentiation between products that were generated by design and those which might have evolved naturally (4). This calls into question the 'artificial' nature of certain products of genome editing.

There has been some consideration of the security implications of genome editing. It has been suggested that genome editing “merely augments and simplifies technology already available for the modification of microbes” and as a result that “it is questionable to what extent it leads to new concerns about deliberate misuse of genome editing in state-sponsored research or for terrorism” (2).

On the other hand, several specific security risks have been identified; for example, that genome editing might have “implications for developing adequate microbial forensics to detect, characterise and track infectious disease outbreaks to distinguish between deliberately induced and natural epidemics” (2).

Engagement with the public

There has also been a substantial consideration of public interests and values around genome editing (1,13).

There have been calls for traditional efforts to ‘educate’ the public through a recognition of a “real need for increased engagement of patients and wider society in general in order to promote a better understanding of the future potential benefits of genome editing” (1).

There have also been calls for more debate as to where socially acceptable applications end and undesirable applications begin (2). This is more in line with the consultative and participatory forms of engagement (13).

There have been efforts to compare public engagement processes in Denmark, France, the UK and the US (13).

Genome editing as a research tool

Genome editing has and is enabling research. These tools have been noted for their “precision, simplicity, speed and low costs” (7). They are “driving scientific research into the functions of specific genes, genetic variations and genetic interactions, leading to significant advances in our knowledge” (7). They have also expanded the range of organisms it is possible to edit (5) and reduced the number of test subjects required in certain research (5). Genome editing has helped us understand human cells and tissues as well as mammalian reproduction and development (13). They have also

⁶ Genome-wide, unbiased identification of double-strand breaks enabled by sequencing.



helped the rapid generation of cellular and animal models, functional genomics screens, for exploring gene expression and regulation, and tracing cells during development (8).

Genome editing in humans

Genome editing in humans can be divided into:

- **Clinical research and applications in human somatic cells** (1, 2), such as functional genomics, disease modelling and drug screening (1); the identification of essential genes in human cells and tumour-specific vulnerabilities (2); reprogramming of adult cells into stem cells (2); prevention of flavivirus reproduction without disrupting the host (2); the influence of epigenetics on regulatory functions and cellular reprogramming in the brain (2); gene- and cell-based therapies (2,5); enabling the exploration of the causes and progression of disease (5); editing the blood stem cells of patients who have a congenital blood disease, metabolic disorder or immune deficiency (14); and improving the capacity of immune cells to attack cancer cells (7).
- **Clinical research and applications in human germline cells** (1,2,5), including both: (a) to deal with disease, such as preventing transmission of inherited genetic diseases (13), or treating diseases that affect multiple tissues (13); and (b) to confer new qualities (enhancement), such as making cells infection-resistant (7);

A number of genome-editing based therapies are in commercial developments, including for sickle cell disease, SKID-X1, X-linked hyper-IgM Syndrome, Haemophilia B, Cystic Fibrosis, HIV, cancers, Duchenne's Muscular Dystrophy, Huntington's Disease, and neurodegenerative diseases (13).

Proposals have been made for both a set of Principles and a Framework for the governance of human genome editing – regardless of whether that be for research, editing of somatic cells, or for heritable traits (13).

In general, the reports support using genome editing on somatic cells under appropriate oversight. This use was generally considered to be sufficiently covered by existing regulatory frameworks (2). There was also broad support for a broader public dialogue about where socially acceptable applications of genome editing end (2).

There is less or very guarded support for using genome editing to make changes that would be heritable. Issues raised included a need to balance individual-level benefits and societal-level risks, parental benefits, unexpected consequences, the need for long-term follow up, possible societal effects, economics and social justice, and a debate around what is a “natural” human genome and degree of human intervention is appropriate (13).

It has been suggested that the benefits would not currently outweigh the risks (6):

Before any intervention in the germline can even be considered, the techniques must be refined until such an intervention represents an acceptably low risk in comparison to the hereditary disease it seeks to prevent.

To this end a model regulatory structure to oversee any such work has been proposed (13).

There is no support for using genome editing for human enhancement in the documents reviewed for this report – with a recommendation that “genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time” (13). Others have called for a moratorium on such applications (5). There was a recognition of the importance of basic research on human embryonic development, and a concern that such a moratorium not impede basic research or the development of somatic therapies (6).



Important issues raised around enhancement include drawing a line between treatment and enhancement, defining normal, or natural in genetic terms, public perception to enhancement, fairness and unfair social disadvantages, and connections with eugenics (13).

There is also a debate around a slippery slope – where permitting research or applications in some areas may enable (or at least complicate preventing) other applications that are not as socially desirable (13).

Genome editing in plant breeding

Genome editing in plant breeding has been connected to several important international policy and regulatory issues, such as sustainability in food production, food security, safety assessment, environmental impact assessment, and possible socio-economic impacts (11). To date it does not seem to have been connected to national security.

Input traits	Output traits
Stacked herbicide tolerance Biotic stress resistance Microbial resistance <ul style="list-style-type: none"> • Major resistance genes • Phytoalexin engineering^a • Novel resistance mechanisms^a • Viral RNA interference or coat protein^a Insect resistance <ul style="list-style-type: none"> • Stacked insecticidal genes^a • RNA interference^a Abiotic stress tolerance <ul style="list-style-type: none"> • Drought tolerance • Water-use efficiency • Cold tolerance • Heat tolerance • Salt tolerance Nutrient-uptake and nutrient-use efficiency Nitrogen fixation (in cereals)^a Phosphorus-use efficiency Carbon fixation <ul style="list-style-type: none"> • Improved Rubisco^a • C4 photosynthesis in C3 grasses^a • CAM in C4 plants^a Post harvest improvements <ul style="list-style-type: none"> • Microbial resistance • Increased shelf-life^a • Reduced bruising^a • Silage stability^a • Standardized quality 	Enhanced nutritional content <ul style="list-style-type: none"> • Micronutrients • Amino acids • Vitamins • Fatty acid profiles • Flavonoids and nutraceuticals Food safety <ul style="list-style-type: none"> • Reduced acrylamide formation^a • Reduced aflatoxin concentrations^a Forage quality <ul style="list-style-type: none"> • Digestibility • Nitrogen protection^a Biofuels and industrial byproducts <ul style="list-style-type: none"> • Ease of processing • Improved biodiesel properties • Advanced biofuels^{a,b}



FIGURE 1: Traits that may be delivered with emerging genome editing technologies.

Reproduced from Figure 8-1, Genetically Engineered Crops and Foods (2016)

Genome editing tools have been used to modify plants, including removing ‘genome-editing reagents’⁷ from genetically engineered crops, and adding or removing traits (Figure 1) (11).

In addition to altering the genetic code of plants, genome editing tools have been used to modify the activity of genes without cleaving genetic material, or the creation of a permanent effect (11). They have also enabled other important developments, such as the creation of artificial and synthetic chromosomes, and targeted epigenetic modification (11).

Recent years have seen efforts to review evidence of the “[m]any claims of positive and negative effects of existing genetically engineered (GE) crops” and “to assess emerging genetic-engineering technologies, how they might contribute to crop improvement, and what technical and regulatory challenges they may present” (11). Several new breeding techniques make use of genome editing, including Site-Directed Nucleases (SDN), oligonucleotide-directed mutagenesis⁸, and variants of genetic transformation (both Cisgenesis⁹ and Intragenesis¹⁰) (9).

Genome editing has been described as “a faster way than conventional breeding techniques to create crops with desirable traits, for example better quality, higher yields, and disease- and pest-resistance” (7).

In plant breeding, genome editing techniques have also been framed as a way to achieve the same modifications as traditional breeding techniques, but much more rapidly (4) and in a more targeted manner (7).

It has also been suggested that genome editing tools could be important in democratising access to modern breeding techniques (7):

Because genome editing is a relatively simple technique, it can be used by smaller plant breeders, provided the regulations are clarified and simplified so that it remains affordable.

There are proposals for more context specific risk assessments of plants bred using these techniques (9).

Regulation

A recurring theme throughout these reports is the need to move from a regulatory regime focused on how something is made (process) to the characteristics of the thing produced (product) (4,9). For example (2):

7 The US National Academies noted “Nucleases that have been customized to target a specific sequence are referred to as reagents”.

8 Where an “oligonucleotide (a small single strand DNA molecule) with a desirable point mutation, similar to the SND-2 donor DNA, is introduced into an animal cell or plant protoplast and incorporated into the target gene via the native DNA repair mechanisms of the cell.”

9 Where “the DNA sequence inserted into the modified plant is an unchanged sequence found in the same species or from a sexually compatible species; usually refers to a complete, functional sequence including the native regulatory and gene sequences.”

10 Where “DNA inserted into the modified plant is re-organised or is used in new combinations, but still from the same species or from a ‘crossable’ species.”



...policy considerations should focus on the applications in prospect rather than the genome editing procedure itself as an emerging technology. It is important to ensure that regulation of applications is evidence-based, proportionate and sufficiently flexible to cope with future advances in the science.

Several reports call into question the appropriateness of existing regulatory regimes for plant breeding in light of modern genome editing technologies. For example, plants may fall under the definition of Genetically Modified Organism even if they have had no foreign genetic material added (4).

There are calls that possible ecological and health-related risks of genome editing products, such as plants, should still be tested on a case-by-case basis and that “only evidence-based scientific risk assessment should be used to make decisions”.

Many reports review specific national or regional regulations governing genome editing and make recommendations as to how they might be updated or amended, for example, in Argentina (9), Canada (9), the European Union (1), Germany (6), the Netherlands (14), South Africa (9), and the United States (11,13, 21).

Implications of developments in the life science and biotechnology

Biological production

Genome editing is playing an important role in helping to use biology as a manufacturing technology. A recent study defined ‘biotechnology products’ as “products developed through genetic engineering or genome engineering” (21). As a result, the impact of genome editing is effectively being framed as the recent history of the biotechnology industry.

A recent review of trends and products in biotechnology highlighted genome editing as a key technical driver for progress in biotechnology (21). Many of the products identified in the review relied on genome editing technologies - both those designed for open-release into the environment (such as genome-edited crops, crops with CRISPR knockouts, bioluminescent trees, genome-edited animals (e.g., polled cattle), animals revived from near extinction or extinction, biosensors/bioreporters, engineered algal strains, genomically engineered microbial communities, and genomically recoded organisms) and contained use (such as transgenic laboratory animals, animal cell culture–derived products, greenhouse crops with CRISPR knockouts, and genomically engineered bacterial strains for fermentation-based products).

There is recognition that risks from a product of biotechnology, including those produced via genome editing, might be context dependent (21):

The level of risk a product presents may depend on how it is sold, distributed, or used. Products that are otherwise safe may pose high risks in the hands of unqualified or malicious users. For example, the safety and biosecurity of do-it-yourself biology (DIYbio) products may be determined by the skill or the intent of the user.

Furthermore, there has been discussion as to how future biotechnology products may not fit comfortably within existing risk assessment approaches. They are expected to increase in complexity and novelty, resulting in fewer comparators to traditional risks.

Regulations that govern biotechnology, and how they impact genome editing, could affect our ability to realise the potential of biological manufacturing. Traditional security-based regulations seek to control access to pathogens (such as the Select Agent Program), regulate their international movement (such as through export controls), or acquire their genetic material (such as through the screening of commercial synthesis of DNA), as well as engage communities perceived as a risk (such



as the citizen science movement). Such measures may not be appropriate for dealing with risks associated with the products of genome editing (21):

...These programs, however, are neither focused nor scaled to address the risks of diverse biotechnology consumer products expected in coming years, and existing consumer-safety regulators like FDA, CPSC, and EPA lack statutory tools to take on this responsibility.

Responsible conduct

There are significant differences among countries “in the definitions of and approaches to the conduct of responsible research”. This led to an effort by scientific academies “to provide clarity and advice in forging an international consensus on responsible conduct in the global research enterprise” (14). Whilst concepts of responsible conduct are not unique to genome editing, it does set a broader framework for responsible research, including activities relevant to this report.

Responsible conduct is important throughout the scientific life cycle including: the research plan; carrying out research; reporting research results; and communicating with policy makers and the public. There are specific actions that can be taken by individual scientists, institutions, professional bodies, research funders, and those promulgating the results. Action is needed in both the public and private sectors. (14)

Genome editing technologies could impact case studies of security in responsible conduct, for example, gain-of-function experiments and the [‘H5N1 Controversy’](#).

Handling dual-use research

The dual-use nature of genome editing technologies has been highlighted (19):

In many cases, research endeavours or technologies that promise the greatest advances also bear the greatest potential for harm. For example, genome editing technologies such as CRISPR/Cas9 could revolutionize many areas of research and industry including therapeutic development, crop improvement, and control of disease-transmitting insects. However, the same advantages that make CRISPR/Cas9 such a powerful tool for researchers – its simplicity, efficiency, and inexpensiveness – could also play into the hands of those who wish to misuse it to do harm.

There has been recognition that recent developments in both tools for research and how results are communicated (for example by the increasing use of pre-print servers) are increasing the challenges associated with maximising benefits whilst minimizing risks (23). It has been suggested that it is possible to identify relevant research prior to publication – during planning stages or when an unusual result is encountered (23). Early identification of dual-use potential enables a wide range of possible actions, including “a decision not to fund the research, withdrawal of funding, classification, mitigation plans, etc.” (23).

Current guidance on how to handle dual-use research highlights the need for all researchers and institutions to be aware of, and comply with relevant laws and regulations (16,18). There is strong evidence that such awareness is not widespread (23).

Researchers, however, have been urged (16):

...not to content themselves with just complying with legal regulations. After all, researchers’ knowledge, experience and freedom give them a special ethical responsibility that goes beyond legal obligations. In addition, research institutions should create framework conditions for ethically responsible research.



Tools have been developed to help researchers accomplish this, including, for example, tools “to aid discussion of the potential for research misuse among scientists and support staff involved in research with biological materials, regardless of their background, discipline, or role” (19,20). These include a series of general rules for working with dual-use biological materials (Table 1). It is to be hoped that the recent development of such resources will help address a historical lack of awareness about dual-use issues, relevant rules and regulations, and the steps scientists might take to address them (23).

There have been some concerns that such measures, especially regulatory measures, “may constrain certain types of research” (23).

Specific actions have been proposed for researchers, research institutions, journal editors, professional societies, national governments, and international coordination (16, 20). However, “no international organization is giving systematic attention to developing policy or guidance regarding the dissemination of scientific information of concern”. Furthermore, “[t]here is no shared, consistent policy among U.S. and international journals for addressing DURC” (23).

A number of reports have framed dual-use issues as a facet of ethical research proposing that at the institutional level the review of research proposals should be undertaken by a strengthened ethics board, rather than a strengthened biosafety board (16,18). Model statutes for ethics committees to oversee dual use research have also been developed (17).

TABLE 1: General rules for working with dual-use biological materials
Be aware and assess your own research
Refrain from research where the potential for harm is disproportionate to the potential benefits
Modify research and/or publications to reduce risks
Report and document risks
Know and use guidelines and safe practices
Be alert and raise concerns (also about others’ research)
Protect sensitive material and data
Train others and serve as a role model

Other proposed approaches include (20):

...a “cradle-to- grave” system in which reviews of experiments at various stages in the research life cycle—from proposal and grant evaluation to publication and communication—would identify and assess potential biosecurity risks

Security implications of science and technology

There is recognition that genome editing technologies might be misused to cause deliberate harm (19):

The potential for misuse is especially apparent with respect to research on human pathogens. Although less obvious, there is also misuse potential in connection with research involving animal and plant pathogens – or involving no pathogens at all.

Genome editing could be used to manipulate human pathogens, possibly making them more suitable for use as a weapon. Genome editing might facilitate those research activities most likely to raise



security concerns - the seven experiments of concern, identified in the 2004 report [Biotechnology Research in an Age of Terrorism](#) (Table 2).

TABLE 2: Seven experiments of concern
Experiments which demonstrate how to render a vaccine ineffective
Experiments which provide pathogens with resistance to therapeutically useful antibiotics or antivirals
Experiments which enhance the virulence of a pathogen or render a nonpathogen virulent
Experiments which increase transmissibility of a pathogen
Experiments which alter the host range of a pathogen
Experiments which enable the evasion of diagnosis or detection
Experiments which enable the weaponization of a biological agent or toxin

Security impacts from genome editing were also identified during a review of life science and biotechnology trends relevant to the ban on biological weapons (15). The most recent such effort, undertaken in 2015, identified several security implications derived from genome editing technologies (Table 3).

TABLE 3: Implications from genome editing for the Biological Weapons Convention
Understanding and altering functions of existing pathogens – in particular, pathogenicity, circumvention of host-immunity, transmissibility and host range, antimicrobial and drug resistance. This enables efforts to combat disease but could also enable the creation of more dangerous pathogens.
Enabling the development of novel pathogens, or agents capable of creating diseases, such as cancer.
Enabling the development of treatments – in particular, novel immunotherapies, cell-based therapies and enhanced viral clearance.
Improving the production of biologically active materials – in particular, in biopharming (or producing important products in plants and animals), biosynthesis, and bio-based production. These compounds could be used to prevent or treat disease, but might also include toxins or other agents destined to be used as weapons.
Altering the susceptibility of potential target populations, such as crops or higher primates, to disease.
Altering the ability of important vectors to transmit disease. This included reducing their ability to transmit disease as a novel form of vector control but also conferring increased resistance to control measures.
Removing toxins from commercially important crops, thereby decreasing their potential to be used to cause deliberate harm.
Improving the efficacy of animal models in studying human diseases, including to facilitate the use of genome editing tools. This would facilitate the efforts of both those attempting to mitigate and instigate disease.

There have also been efforts to develop more structured frameworks for assessing the impact of advanced biotechnologies. One such framework (see Annex A), was built to consider how synthetic biology technologies are affecting biodefence. It looks at specific biological engineering tools and how



they impact both malicious use and mitigation efforts (22). Genome editing was one of the core technologies to be included. The framework has yet to be populated.

As the authors note “the framework may be useful for a broader array of contexts than those addressed in this study” and it may be useful during efforts to consider the security implications of genome editing.



Part II: Security implications of genome editing technologies

Gene editing and national security threats

Perhaps the highest profile publication connecting genome editing and national security was in February 2016 when the then Director of US National Intelligence [testified](#) that these technologies are relevant to weapons of mass destruction and a threat to national security:

Research in genome editing conducted by countries with different regulatory or ethical standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products. Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications. Advances in genome editing in 2015 have compelled groups of high-profile US and European biologists to question unregulated editing of the human germline (cells that are relevant for reproduction), which might create inheritable genetic changes. Nevertheless, researchers will probably continue to encounter challenges to achieve the desired outcome of their genome modifications, in part because of the technical limitations that are inherent in available genome editing systems.

The reaction of the scientific community to this testimony was moderate, with commentaries in both [Science](#) and [Nature](#) underlining broader concerns over the societal implications of genome editing. The latter noting:

The headline message might scream ‘overreaction’ — and indeed most serious science commentators seem to have assumed as much and ignored Clapper’s hyperbole — but the terms he used to describe the technology seem uncontroversial.

The *Nature* commentary went on to detail how the specific issues raised in the testimony fit closely to the views of those driving developments in genome editing (in terms of rapidly becoming broad distribution, lowering cost in research, and accelerating the pace of development). The commentary also highlighted concerns over gene drives, the transformative nature of the technology, and the debate over human germline editing. It concluded by highlighting how much more attention had been given to the benefits of genome editing rather than to any risks.

How genome editing might impact national security

The public version of the US testimony provided few insights into how genome editing might impact national security and why it was being perceived as such a threat.

Commentators soon highlighted potential security implications. A [report](#) in STAT news linked the testimony to earlier concerns over gene drives. A [report](#) in the *MIT Technological Review* highlighted potential risks from novel pathogens, accidents, and a connection between security concerns and heritable genome editing or enhancement. These security implications were discussed in more detail in an [article](#) in the *Bulletin of Atomic Scientists* a few months later.

The US Congressional Research Service has since published an [assessment](#) of the potential for genome editing to be used to enhance pathogens, concurring with the finding of an earlier meeting that “should a biological weapons program be started today, these technologies would likely become a part of it”.



A subsequent [article](#) in *Health Security* highlighted the potential to use genome editing tools to develop neurological weapons by enhancing traditional neurotoxins or infectious agents that could affect the nervous system or “directly act[ing] on genes in the brain to alter neural phenotypes that influence cognition, emotion, and behaviour”. Such a risk could be compounded if ‘hacking the brain’ for other purposes, such as therapy or recreation, became more commonplace as seemingly suggested by the authors who believe “it is likely that attempts at neuro-hacking will increase in both number and sophistication”.

The feasibility of different possible security impacts is reviewed in a forthcoming article by Esvelt and Millett in the Scientific and Technical Review of the World Organization for Animal Health (in press). No clear contender is identified. This article also develops concepts of heritable genome enhancement – moving past discussion of enhancing soldiers, for which it raises technical, logistical, and conceptual problems, to consider the possibility that a widespread application of gene editing might offer distinct economic advantages at the national level. If these advantages were significant, it is argued that this might represent a national security concern.

Security concerns from genome editing, however, did not begin with, nor end with, the February 2016 testimony.

Security concerns before the US intelligence testimony

The security impact of genome editing technologies had been raised prior to the US testimony. For example, a November 2015 [commentary](#) in *Nature* noted that genome editing was one of a range of enabling “tools and approaches [which] are greatly expanding the possibilities for genetic engineering, including for would-be terrorists”.

TABLE 4: Security Implications from genome editing technologies	
Beneficial , increasing our capacity to deal with disease regardless of cause, including:	
<ul style="list-style-type: none"> Improving tools to study features of hosts and targets in drug delivery; Development of new drugs and therapies, such as gene therapy; Improved understanding of antimicrobial and drug resistance; and Developing alternatives to biological materials that pose much less of a proliferation risk, such as castor beans without Ricin. 	
Malicious , furthering the aims of those who seek biological weapons, including:	
<ul style="list-style-type: none"> Concealing the fact an agent might have been edited; New types of agents, such as through gene drives; Adding functions to existing weapons agents; Designing advanced weapons agents; Producing bioweapons agents, such as through biosynthesis, bio-based production, or biopharming; or Altering the properties of a bioweapon’s target, including resistance characteristics. 	

Possible security implications had also been considered at the international level. For example, the Biological Weapons Convention had [examined](#) genome editing tools during both expert and policy processes in 2014 and 2015. States discussed positive implications from genome editing, for example



in enabling the development of medical countermeasures. They also highlighted that these tools could also enable gain-of-function research, which could result in a potentially pandemic pathogen.¹¹

As discussed in Part I, in late 2015 the IAP conducted a review of trends in science and technology relevant to the Biological Weapons Convention. This [highlighted](#) both beneficial and malicious security implications from genome editing (Table 4).

Subsequent security concerns

Genome editing appeared again in the 2017 [testimony](#) from the US Director of National Intelligence, but this time, framed not as a weapons of mass destruction threat but as an emerging and disruptive technology (along with artificial intelligence, the internet of things and next-generation semi-conductors):

The development of genome-editing technologies is accelerating the rate at which we can develop new approaches to address medical, health, industrial, environmental, and agricultural challenges and revolutionize biological research. However, the fast pace of development and broad range of applications are likely to challenge governments and scientific communities alike to develop regulatory and ethical frameworks or norms to govern the responsible application of the technology.

More pointed security concerns over genome editing seem to persist in the US as a Department of Defence [report](#) suggests they are currently working on a new national policy for genome editing and synthesis.

Genome editing security concerns – a self-fulfilling prophecy?

It has been [argued](#) that highlighting possible security concerns associated with genome editing might increase the likelihood of it being applied to cause deliberate harm in the future.

On the other hand, others have [suggested](#) that a vibrant debate around possible security implications is important because the technology will diffuse anyway.

Genome editing and citizen science

Security concerns have also been voiced over the possible misuse of genome editing technologies outside of traditional science settings. For example, a March 2016 [commentary](#) in *Nature* highlighted several such publications. The article argues that this is a notable misrepresentation of current capabilities:

... the techniques and expertise needed to create a deadly insect or virus are far beyond the capabilities of the typical DIY biologist or community lab. Moreover, pursuing such a creation would go against the culture of responsibility that DIY biologists have developed over the past five years.

The article continues to provide numerous examples of the types of research actually being done in community labs and the efforts of the citizen science community to develop and promulgate a culture of responsibility.

¹¹ A potential pandemic pathogen (PPP) is one that satisfies both of the following: (a) it is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and, (b) it is likely highly virulent and likely to cause significant morbidity and/or mortality in humans. See: <https://www.phe.gov/s3/dualuse/Documents/P3CO-FinalGuidanceStatement.pdf>



In addition, others have [called into question](#) whether the genome editing capacities readily available to citizen scientists could be applied to create high-impact biological weapons.

Genome editing and mitigating security concerns

Throughout much of the commentary on possible security implications from genome editing, there appears a recurring theme that these techniques and technologies can help address security concerns. Along with other enabling technologies, genome editing can enable medical countermeasure development, for example. As the US congressional Research Service has [noted](#) “this technology may simultaneously address some national security concerns while raising others”.

To this end, it is important that the application of genome editing technologies is carried out responsibly; for example, consistent with the responsible conduct in the research enterprise as captured by the IAP report discussed in Part I. It may also be possible to shape genome editing technology itself to reduce risks of deliberate misuse, or to develop tools that help us better understand and manage security-related risks.

To help ensure the responsible and safe development of genome editing technologies, DARPA has established the [Safe Genes](#) programme “to facilitate the safe and expedient pursuit of advanced genome editing applications, while also providing the tools and methodologies to mitigate the risk of unintentional consequences or intentional misuse of these technologies”. According to a [press release](#), to date the programme has funded seven projects.

Genome editing in a broader context

In Part I, several publications from the scientific community framed genome editing as one enabling tool that is changing the face of modern life science. The security implications of genome editing also need to be considered within a wider context.

A broader framing of security

A month prior to the US testimony, an [article](#) in the Cypher Brief linked advanced biotechnological tools, like genome editing, to a much broader framing of national security that included resource security, energy security, manufacturing security, data security, and environmental security, as well as advanced biological weapons.

This broader security framing was also picked up by the US President’s Council of Advisors on Science and Technology later in the year, who [called](#) for biodefence strategies that address “a much wider array of novel and ever-changing biological threats that may be impossible to fully anticipate”.

A broader understanding of the technological environment

[Articles](#) that followed the US testimony highlighted the unusual step of singling out a single technology – rather than considering their collective impact. More recently a [report](#) into growing interconnectivity and smart automation of labs identified genome editing as one of a set of related technologies changing how research is performed. Genome editing’s security impact might therefore be dependent up how it is used with other technologies. This may necessitate a more comprehensive assessment of the impact of developments in science and technology.

There is a considerable body of work looking at such impacts on security issues - such as the capacity to acquire or use biological weapons. For example, the IAP [noted](#) changing trends in science



and technology “could also facilitate almost every step of a biological weapons programme and technological barriers to acquiring and using a biological weapon have been conspicuously eroded”.

These technology assessments focus on broader trends within the conduct of science and technology – rather than individual technologies. A March 2016 article highlighted four relevant trends in the conduct of the life sciences:

- “increasing pace of advances in bioscience”;
- “increasing convergence of biology and biomedicine with chemistry, engineering, mathematics, computer science and information theory”;
- “increasing diffusion of capacity in biology and biomedicine around the world, particularly in emerging economies such as China and India”; and
- “increasing opening up of science with new tools like wikis, blogs and microblogs altering how information is gathered, handled, disseminated and accessed; and amateur communities, scientific out-reach and educational toys increasing access to hardware for wet work in the life sciences”.

When considering the security implications of genome editing, it may be useful to consider how this particular technology is impacting these broader trends rather than its direct security impact. For example, a May 2016 [report](#) on synthetic biology in the context of the Biological Weapons Convention used the adoption and commercialisation of CRISPR-based gene editing tools as an example of the increasing pace of advance.

Equally, the game changing nature of gene editing has been noted in other closely connected fields. For example, when the European Commission developed its risk assessment methodology for synthetic biology, it [recognised](#) genome editing as a novel capacity when compared with earlier genetic engineering capabilities.

Frameworks for assessing security implications

When the IAP conducted its review of trends in science and technology relevant to the Biological Weapons Convention in 2015, it considered how advances might enable or mitigate the individual steps a bad actor would be required to pursue to acquire or use such a weapon.

Example – acquisition of a weapon agent

A July 2017 article defining the synthetic biology supply included an assessment of the impact of genome editing on an action necessary for someone to acquire a biological weapon:

A person with basic knowledge of molecular biology and experience with gene editing techniques has access to a number of options from which to source desired material and design a fully functioning biological system.

Hence, the authors of this report are illustrating how genome editing has helped to expand potential routes to the acquisition of a biological weapon.

A similar approach was adopted by the US National Academies when developing a framework to consider the biodefence implications of synthetic biology (Annex A). Ongoing efforts will consider how technical developments will impact the efforts of bad actors – in particular how they impact the use of relevant technologies, the feasibility of adapting them for use in a weapon, or on the required attributes of the actor. It will also consider their impact on deterring or preventing such a weapon being developed, recognizing when an attack has taken place, or identify the responsible parties.



Example – Impact on the use of a technology

In November 2016 the US President’s Council of Advisors on Science and Technology, considered the impact of advanced biotechnologies on efforts to protect against biological attacks. They [identified](#) how genome editing impacted the use of technologies for biological weapons purposes.

First, they highlighted four limitations of first generation tools for genetic modification: (1) “the procedures for assembling recombinant genes were time-consuming”; (2) “the available regulatory-control sequences were limited”; (3) “targeting genetic modifications to specific locations in the genome of a living cell required complex procedures”; and (4) “delivering DNA to specific cell types was often challenging”.

They then detailed how recent developments had changed the status:

Scientists can now cause virtually any DNA sequence of interest to be cut (genome cleavage), modified to a new sequence (genome editing), or bound by a regulatory protein (gene activation or repression). Moreover, the process is rapid and efficient: genetic engineering that previously required many months or years can now be performed in days or weeks.

Such a structured framework may be of use when considering the security implications of genome editing.

Genome editing, regulations and oversight

Overwhelming regulatory capacity

A different type of security impact from genome editing might be overstressing current regulatory arrangements. Genome editing could [result](#) in a rapid increase in the number of activities covered by regulations. This might make it difficult for regulatory structures to keep pace, as noted in an August 2016 [article](#) on risk assessment of synthetic biology.

There have been efforts to update oversight and regulatory arrangements in light of developments such as genome editing. For example in the UK, Biosecure hosted a one-day workshop on genome editing and national security in July 2016. The meeting brought together national experts from the life sciences, academia, industry, bioethics, security, export controls, as well as representatives from several relevant government departments. Participants discussed how best to continue to develop genome editing tools safely and securely. It also identified several generic activities for strengthening current arrangements.

Circumventing regulatory controls

Genome editing, when combined with other emerging technologies and techniques in the life sciences, may [enable](#) bad actors to side-step current regulatory controls (Figure 2). A 2017 US Congressional Research Service [report](#) agreed: “it may be possible to use gene editing to circumvent current mitigation strategies”.

Outpacing international norm setting

If it is difficult for national oversight and regulatory systems to keep pace with technical developments like genome editing, it is even more difficult at the international level. In many cases the architecture in place may complicate efforts to adapt to major shifts in the technical reality. For example, the review of science and technology used to review the operation of the Biological Weapons Convention only occurs every five years. It has long been recognised that this is insufficient to keep pace with the



rate of scientific and technological change. As a result, between 2012 and 2015 annual reviews were attempted.

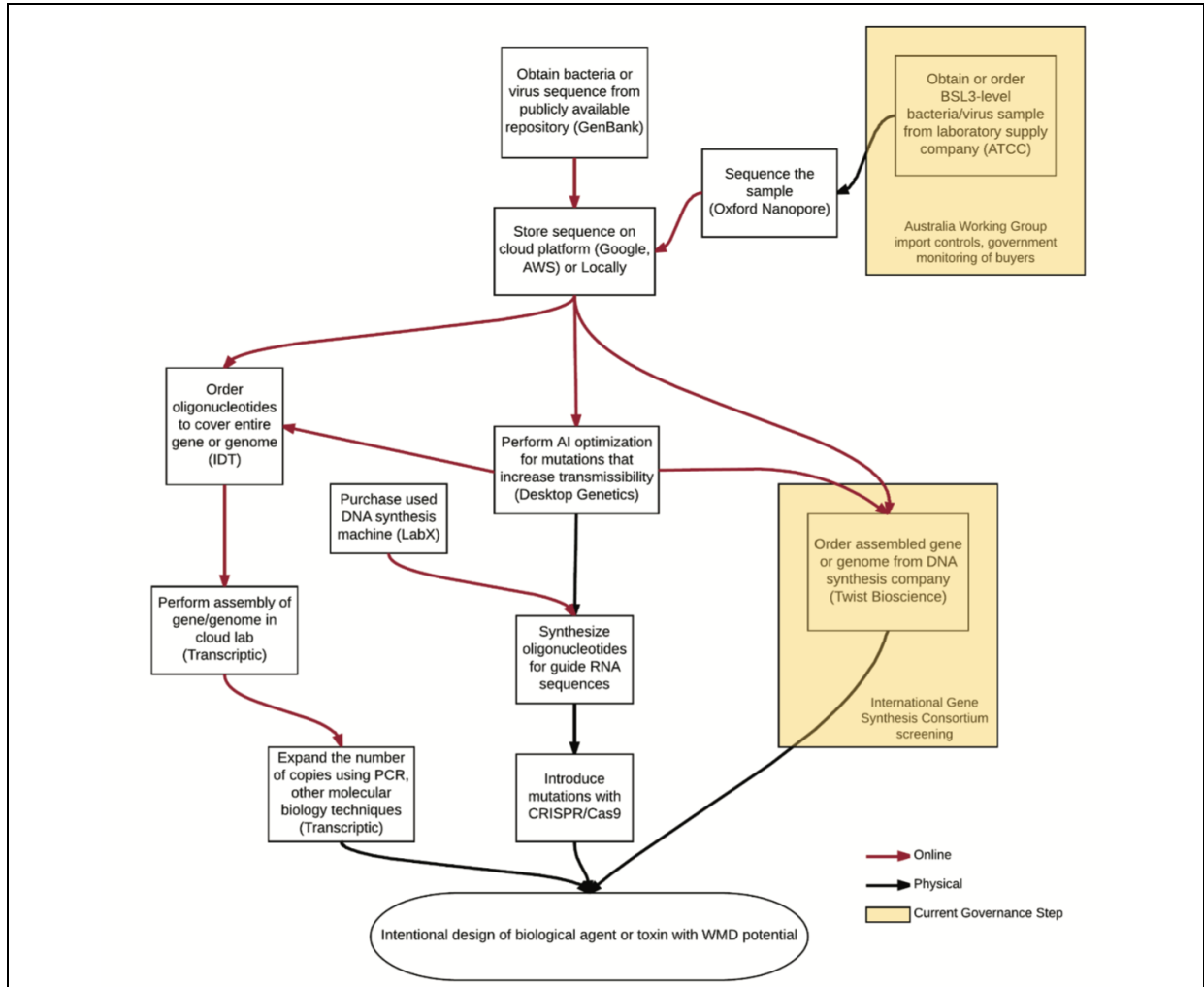


FIGURE 2: Exploiting the gaps

Given advances in DNA synthesis techniques and the advent of robotic cloud laboratories, one may find ways to circumvent current governance barriers. Example companies to complete each step are listed in parentheses. (Reproduced from: The Intelligent and Connected Bio-Labs of the Future: Promise and Peril in the Fourth Industrial Revolution)

Prior to its five yearly high-level review in 2016, the need to consider the implications of genome editing for the Biological Weapons Convention was highlighted in a [Nature commentary](#). The speed of adoption of genome editing technologies, and their impact on the way science was being done, was highlighted as an example of why this treaty needed a more comprehensive and responsive mechanism to review scientific and technological developments.

The 2016 review conference failed to renew any process for more regular reviews of the science and technology. This has led to [calls](#) to take immediate action to strengthen this regime.



Undermining traditional security approaches

A July 2016 [commentary](#) by a former senior US official argued that the dramatic changes in the conduct of science being driven by enabling technologies such as genome editing, could challenge the traditional non-proliferation and security approach, especially where it relies on technology controls.

Similar concerns were included in a [review](#) of advanced genome editing by the US Congressional Research Service which noted “export control regimes and international agreements designed to limit proliferation may be ill-suited for addressing national security concerns raised by gene editing”.



Part III: Gene drives

Policies, positions and guidance from the scientific community

Many of the reports and resources discussed in Part I of this document made specific reference to gene drives – describing what they are and how they work (3,5,9,11,12,19), how they might be applied (5,19), and identifying key experiments in their development and proof of concept (11,19).

Several reports noted that gene drives do occur in nature but that developments in genome editing now enable their programming. (3,5)

Possible applications identified for gene drives include:

- **Public health**, such as for pest control (2) or vector control (2,3,5,10), which can help manage diseases like dengue (2,12), malaria (2,12), Zika (2), Lyme disease (2), schistosomiasis (2),
- **Animal health**, such as to manage diseases like avian malaria (12);
- **Agriculture** (3,10), such as by increasing agricultural output (12), or eliminate herbicide or pesticide resistance (9);
- **Environmental protection**, such as to protect against invasive species (3,9,10) and protect biodiversity on islands and in rangelands and forests (12); and
- **Research**, such as for a model for gene drive use in vertebrates (12), or simply as an aid to generating animals with complex genotypes for studies in basic biology.

Several challenges confront the application of gene drives, including:

- The size of an initial release needed to make a trait dominant in a population in a very limited number of generations; (5)
- The importance of not conferring other significant disadvantages on affected offspring, thereby selecting against the desired trait; (5)
- Potential negative reactions by the public (3,10), including by an association with GMOs (12)
- Understanding impacts prior to a release, including through better ecosystem modelling (2,3);
- Questions over the efficacy of gene drives, such as: the potential development of resistance (2,3); genetic diversity in natural populations providing sources of natural resistance (2); a need for more data on genetic stability in the wild and the impact of alternative DNA repair pathways (2); and
- Trade implications (3).

Key differences between gene drives and other biotechnologies have been identified, including: increasing the impact that a small group may be able to deliver (14); increasing the number of actors with potential access to such a powerful technology (14); the potential to undo alterations using reversal drives (14); and an intent to become pervasive in the environment (9).

A broader debate over whether we should use gene drives is also underway (as opposed to whether we can). Relevant values being considered included potential harm and benefits to humans or the environment, justice issues (3,12), and the impact of intellectual property (3).

Risks

Concerns over the release of gene drives primarily focus on either: (a) under what conditions would it be appropriate to release a gene drive in the wild, including for field trials; or (b) how to prevent the accidental release of a gene drive during research and development. Much less attention has been paid to the possibility of a malign actor deliberately releasing a gene drive to cause harm.



There are efforts to consider how risks connected to gene drives should be assessed and how existing risk assessment methodologies might need to be updated (12).

There was a broad understanding that a thorough risk assessment would be needed before any intentional release or field trial should be attempted (2,5,12). A phased testing approach has also been suggested to ensure research does not outstrip efforts to consider the implications (2,12).

A number of practical containment measures for research and development are discussed. (11,14) These include:

1. **Molecular approaches**, such as:
 - a) Splitting the drive across two separate genetic constructs (3,11);
 - b) Using DNA-free or transgene-free approaches where “only proteins and RNAs are introduced into the plant to accomplish gene editing” (11);
 - c) “[U]sing synthetic target sequences that are not in natural populations and therefore could not spread to wild organisms” (3);
 - d) “[T]argeting unique sequences which are very specific to the target organism to avoid a gene drive spreading to closely related species” (3);
 - e) Choosing a threshold drives - which has a low ability to spread (3); and
 - f) Designing drives that would stop after a few generations, such as daisy chain drives (3).
2. **Physical approaches** (3), such as:
 - a) Using the WHO guidance on research involving genetically-modified mosquitoes (3);
 - b) Avoiding transferring gene drive modified organisms between labs (3); and
 - c) Ensuring work is undertaken with appropriate containment provisions (3).
3. **Safeguards** (3), such as:
 - a) “an immunisation gene drive to block the spread of unwanted gene drives by pre-emptively altering the target sequence thereby preventing the gene drive from spreading” (3);
 - b) “a reversal gene drive designed in parallel with any gene drive experiment to overwrite any unwanted changes” (3)
 - c) “trialling a gene drive using a benign change to enable the effectiveness of a gene drive spread to be studied prior to a release” (3); and
 - d) “ecological modelling to help predict the potential consequences resulting from a gene drive release” (2,3).

Several reports address the issue of detection of gene drives, for example noting that current capabilities for environmental monitoring may need to be strengthened to be able to detect an accidental or deliberate release.

Security and dual use risks are also considered. Potential malign or malicious applications of gene drives include being used:

...to deliberately deliver new diseases or toxins to humans. They could also be employed to cause damage to agriculture, for example, by eliminating pollinators or by rendering plant pests resistant to insecticides. (19)

There is also some consideration as to how to address the risk of deliberate misuse. For example (12):

Gene drive research raises concerns about biosafety, biosecurity, and potential dual use of the technology. The scientific community, including individual researchers, institutions, and funders, have an obligation to engage in conversations with policy makers about best practices to safeguard against unintentional or intentional misuse of gene-drive modified organisms. Safeguards will be aided by rigorous attention to confinement and containment protocols in



laboratory and field tests; active awareness about the potential for misuse; and participation in education and training programs about the dual use potential of gene drive research. Governance mechanisms need to be in place to address questions about the biosecurity implications of gene drive research and consider developing mitigation strategies that are not dependent on the underlying technology.

Transparency and engagement with the publics

There is a heavy focus on ensuring research and development is carried out transparently. It has been argued that:

Transparency will ensure compliance with the BWC, accelerate the science by encouraging international collaborations, and promote early deliberations and community guidance of potential applications in public health, sustainable agriculture, and ecological conservation.

There are calls that the experimental designs of all gene drive research should be publicly disclosed (14).

Other reports call for active engagement to be built upon this transparency (5,10,12). For example, “to conduct social discourse on the use of this technique and where its boundaries should lie.” (5) A framework for conducting engagement has been proposed (12).

Regulation

Several reports discussed how gene drives relate to current regulatory regimes, including in Australia (3), Brazil (10), Canada (10), Germany (5), the European Union (10), Norway (10), and South Africa (9).

A number of regulatory approaches, separately or collectively, were identified as being of potential use for gene drives, including: basing regulation on the product, rather than the processes used to create it; increased focus on measuring persistence of organisms; and replacing risk assessment with risk and benefit assessment (10).

Extracts from publications on the security implications of gene drives

Concerns over the possible security implications of gene drives stretch back to the August 2014 [publication](#) of key technical breakthrough making them a reality. For example, gene drives had been [considered](#) at experts meetings of the Biological Weapons Convention since August 2014.

Intergovernmental treaties

In 2014, the Biological Weapons Convention was [briefed](#) on possible security implications “the same week as key technical and policy publications were released.” Identified security implications included: “gain-of-function enabling ability to host diseases”; “suppression of crops and livestock in traditional agriculture”; “suppression of pollinators and other keystone species”; “immunization drives may protect self and allies from effects”; and “reversal drives may be withheld for economic or political gain”.

In a 2015 technical presentation by Switzerland on gene editing, a section on gene drives highlighted:

...potential dual use risks, including: making it more difficult to detect genetic manipulation; irreversibility or hard to calculate consequences in other species; and issues associated with greater access to such capabilities.



Technical press

Security concerns have not been limited to security treaties. They have also been the subject of commentaries in the technical press. In August 2014, accompanying the key technical publication, a second [article](#) in *Science* outlined the need for regulation of gene drives and discussed their implications for society, including possible security implications such as targeting wild organisms, crops and livestock. An [article](#) in *Science* later the same month argued: “[r]egulations are effective only for legitimate organizations and nations, whereas gene drive technologies can, in the wrong hands, potentially be used for malicious purposes”. The author suggested that it was necessary “to call upon the scientific research community to prevent the disclosure of exact instructions on making specific gene drives in scientific manuscripts or patent applications”. A [response](#) from the authors of the first *Science* commentary argued that: “treating information related to gene drives as classified would be technically ineffective and politically counterproductive”.

Some have argued that both the promise and perils of gene drives had been overhyped. For example, an October 2016 [article](#) in the *Bulletin of Atomic Scientists* reported initial findings from interviews with scientists using genome editing tools which suggesting that they “can require particular kinds of skills, resources, equipment, and infrastructure that are not accessible to all—making the application of CRISPR for bioweapons purposes perhaps not as easy as it might seem at first glance”. The authors also argue that these technical barriers mean that it is more likely that states explore possible weapons applications for gene drives than terrorists.

Concerns over security implications continued to arise over the coming year, for example with security interest in the technology, including by the US Department of Defence, Federal Bureau of Investigation and the Biological Weapons Convention, being discussed in a November 2015 [article](#) in STAT news.

Possible security concerns were posited as a possible cause of the US intelligence testimony branding genome editing a national security threat in 2016. Leading gene drive scientists quickly [called into question](#) the utility of gene drive-based biological weapons.

Biorisk management

There has also been work on practical biorisk management for gene drives. A suite of containment measures had been proposed in an August 2015 [article](#) by gene drive researchers, with a recommendation to employ at least two of molecular, ecological, reproductive and barrier containment approaches. Such measures could also put additional barriers in the path of anyone intent on acquiring or using gene drives to cause deliberate harm. These concepts have been further developed since, for example, through an [article](#) detailing appropriate molecular containment techniques and a demonstrated ability to produce a reversal drive in yeast.

This has since been complemented with proposals for adaptive biorisk management – intended to provide practical tools to address biosafety and biosecurity risks from novel synthetic constructs (see Annex B). Gene drives has been [proposed](#) as an initial test case for a more adaptive approach.

Managing safety and security concerns from gene drives has continued to attract considerable security attention and even funding in the US. Much of the DARPA [Safe Genes](#) programme is intended to address these risks (see Part II). A July 2017 commentary in *Nature* also highlighted that IARPA (the US intelligence community’s advanced research projects agency) has “a planned funding programme for detecting genetically modified organisms that are potentially harmful, including ones that contain gene drives”. Security implications have been considered by the JASONS,¹² which is expected to produce a classified report on the subject for the US government. Concerns have been

¹² JASONS are “a group of elite scientists that advises the US government on national security”.



[raised](#) over the amount of US defence money being invested in gene drive research, in particular how such investment may be perceived in other countries.

Several countries have already adopted gene drive specific guidance and regulations, including [the Netherlands](#), [Germany](#), and the [United Kingdom](#). Whilst security issues are not currently a major focus of these documents, they do place potential barriers in the path of a would-be proliferator. They also might provide a foundation on which future biosecurity guidance might be built.

Developing safety and security risk mitigation measures has not been the preserve of governments. Following an attempt to develop gene drives by an undergraduate team, the International Genetically Engineered Machines competition (iGEM) has created gene drives [policies](#). iGEM developed and implemented an oversight framework for any team granted special permission to work on gene drives. This requires teams to demonstrate to international gene drive researchers and the competitions Safety and Security Committee that they appreciate the risks involved and are taking appropriate risk mitigation measures, including implementing the full suite of measures proposed by gene drive researchers in 2015.



Annex A:
**Proposed Framework for Identifying Potential
 Biodefense Vulnerabilities Posed by Synthetic Biology**
 (Reproduced from the US National Academies [report](#) of the same name)

Design	Build	Test	Synthetic Biology Technologies and Applications	Factors to Assess Capability for Malicious Use			Factors to Assess Capability for Mitigation			
				Use of Technology	Use as a Weapon	Attributes of Actors	Deterrence and Prevention Capabilities	Capability to Recognize an Attack	Attribution Capabilities	Consequence Management Capabilities
			Automated Biological Design							
			Metabolic Engineering							
			Phenotype Engineering							
			Horizontal Transfer and Transmissibility							
			Xenobiology							
			Human Modulation							
			DNA Construction							
			Editing of Genes or Genomes							
			Library Construction							
			Bootstrapping of Engineered Constructs							
			High- Throughput Screening							
			Directed Evolution							

FIGURE 1 Committee's Proposed Framework. Committee's proposed framework with factors to consider presented as columns. Synthetic biology technologies and applications to consider are presented as rows. Shading shows which phases of the Design-Test-Build cycle the synthetic biology technologies align with most closely.



Annex B: An adaptive risk management approach

(Reproduced from Lunshof & Birnbaum. [Adaptive Risk Management of Gene Drive Experiments: Biosafety, Biosecurity, and Ethics](#). Applied Biosafety, 22(3), 2017.)

Step 1

Adaptive Risk Assessment

- Assess the rationale of the experiment. Include scientists.
- Perform analysis of the justification for the experiment. Include scientists and ethicists.
- Explore alternative experimental models: can comparable results be obtained through other means than the proposed technologies? Include scientists, ecologists or other relevant professionals and ethicists.
- Define risk in terms of biosafety, biosecurity, environmental impact, human / animal health impact. Confirm with scientists, ethicists, biosecurity experts, ecologists, public health professionals and veterinarians.

Step 2

Adaptive Risk Management Strategy for Gene Drive Experiments

Define Risk in terms of biosafety, biosecurity, environmental impacts, human and animal health impact.

Primary Control: Molecular Containment/Ecological Containment

The internal controls that an organism has to inhibit transmission or release of an organism. This aspect of control is the most crucial in preventing uninhibited spread. This can be natural or can be introduced through recombinant means.

Secondary Controls: Facility Containment and Associated Practices and Procedures

Agent	Containment	Description
RG1 agent/technology where negative Biosafety or Biosecurity outcomes could be present.	Enhance containment to either BSL1+ or BSL2	Incur additional practices and procedures following BSL2 procedures in a BSL1 laboratory (BSL1+) or work within a BSL2 laboratory with BSL2 practices and procedures
RG2 agent/technology where negative Biosafety or Biosecurity outcomes could be present.	Enhance containment to BSL2+ or BSL3	Incur additional practices and procedures following BSL3 procedures in a BSL2 laboratory (BSL2+) or work within a BSL3 laboratory with BSL3 practices and procedures

Tertiary Controls:

Additional Controls above base-containment level and in addition to the molecular/environmental controls. These additional practices and procedures would be enhancements above and beyond the standard requirements seen in biocontainment. Examples of these controls would include enhanced engineering and administrative controls including alternative waste treatment practices, specialized containment controls, and specialized decontamination processes.

Step 3

Evaluation and Adjustment

- Evaluate risk management strategies. Include scientists, biosecurity experts and ecologists.
- Assess options for risk control by other means than containment. Include scientists, ethicists, biosecurity experts, ecologists, public health professionals and veterinarians as needed.

Step 4

Periodical Reassessment

- Review and periodically reassess the experiments. Include scientists, ecologists, and biosecurity experts.
- Review rationale and justification for continuation of the experiments. Include scientists, ecologists, ethicists and other relevant professionals.

