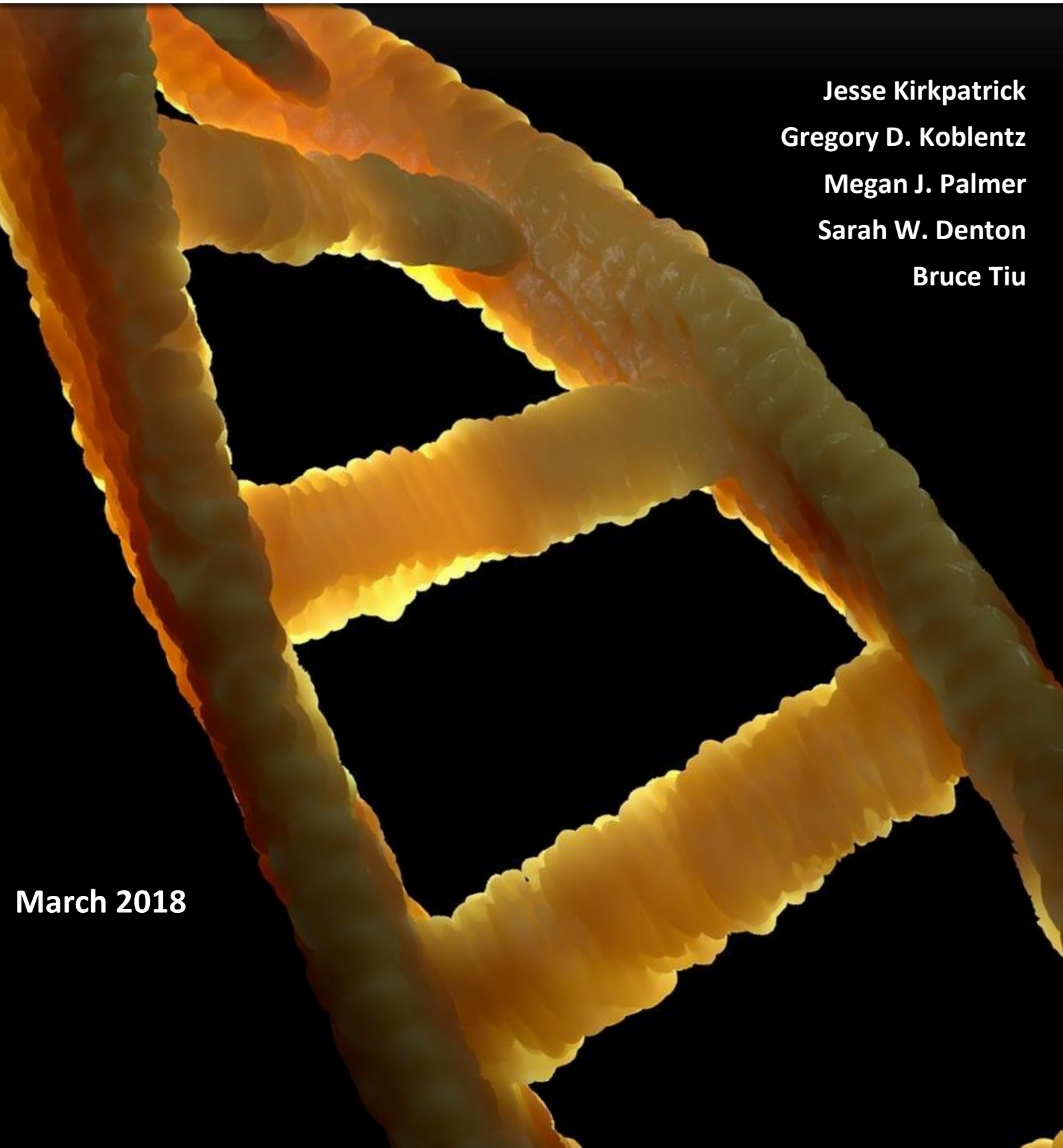
BIOTECHNOLOGY GOVERNANCE: LANDSCAPE AND OPTIONS

Editing Biosecurity Working Paper No. 2



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STUDY OVERVIEW

The rapid advancement of genome editing techniques, such as CRISPR, and its adoption by a broad range of users has sparked concerns that both state and non-state actors may seek to leverage peaceful advancements in genome editing for their own hostile purposes. Researchers from George Mason University and Stanford University initiated this two-year multidisciplinary study, *Editing Biosecurity*, to explore critical biosecurity issues related to CRISPR and related genome editing technologies. The overarching goal of this study is to present policy options and recommendations to key stakeholders. 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 and three research assistants for *Editing Biosecurity* were assisted ' core research group of fourteen subject-matter experts with backgrounds in the life scie industry, policy, ethics, and security. The centerpiece of the study were three invitation-o workshops that brought together the core research group for structured discussions of the benefits, risks, and governance options for genome editing. To support these workshops, the study leads prepared two working papers on risk assessment and governance and commissioned five issue briefs on key topics.

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

A list of project participants can be found in the project's final report, *Editing Biosecurity: Needs and Strategies for Governing Genome Editing*, **which is available at: www.editingbiosecurity.org.**

CONTENTS

Scope of Work

This is the second working paper authored by the Editing Biosecurity project's research team. The overall purpose of the working papers is to examine the state-of-the-art for assessing the risks and benefits of emerging dual-use technologies and to examine how current policies used to govern dual-use technologies could be applied or adapted to genome editing technologies. The working papers were intended to inform and guide discussion in the study's two workshops and lead directly into development of the study's final report.

This working paper presents a draft framework for assessing governance options for genome editing. The draft framework draws from best practices identified by the research team in the first working paper.[1] The framework identifies some criteria that provide a common frame of reference and is intended to facilitate an assessment of the risks, benefits, and governance landscape of genome editing technologies, and draw comparisons across different applications, domains, and industries. The framework is accompanied by scenarios that offer concrete cases to serve as the point of departure for discussion.

Our goal is to use the framework and associated scenarios to facilitate discussion with the objective of generating potential governance options. This framework provides an initial basis from which to select from a menu of options for governing the technology. The second section of this working paper presents a typology of policy options that have been used to govern dual-use biotechnologies and notional applications of illustrative governance options to genome editing. This section is based on past experiences developing and implementing options for governance of dual-use biotechnologies such as recombinant DNA, synthetic biology, dual-use research, and "gain of function" experiments. The evolution and evaluation of the regimes governing biosafety and biosecurity in the United States is contained in Appendix A. This working paper provides a foundation for further work assessing the viability of different governance options for genome editing and their implications for policy and practice.

Introduction to the Draft Framework: Parameters for Developing and Assessing Governance Options

This section of the working paper briefly explicates the draft framework's parameters that the research team has identified. These parameters are intended to help identify and assess governance options related to four broad categories of security-relevant policy goals associated with genome

[1] These include National Research Council (NRC), Biotechnology Research in an Age of Terrorism. Washington, DC: National Academies Press; 2006: doi.org/10.17226/10827; Institute of Medicine and National Research Council (NRC), Globalization, Biosecurity, and the Future of the Life Sciences. Washington, DC: National Academies Press; 2006: doi.org/10.17226/11567; Garfinkel MS, Endy D, Epstein GL, Friedman RM. "Synthetic genomics: options for governance," Industrial Biotechnology 2007; 3(4); Tucker J.B. ed., Innovation, Dual Use, and Security: Managing the Risks of Emerging Biological and Chemical Technologies. Cambridge: MIT Press; 2012; National Science Advisory Board for Biosecurity (NSABB) Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research. National Institutes of Health: Office of Science Policy; 2016; Gryphon Scientific, Risk and Benefit Analysis of Gain of Function Research: Final Report; April 2016: http://www.gryphonscientific.com/wp-content/uploads/2016/04/Risk-and-Benefit-Analysis-of-Gain-of-Function-Research-FinalReport.pdf; National Academy of Science, Engineering, and Medicine (NASEM), A Proposed Framework for Identifying Potential Biodefense Vulnerabilities Posed by Synthetic Biology. Washington, DC: National Academies Press; 2017; and Cummings CL, Kuzma J. "Societal Risk Evaluation Scheme (SRES): scenario-based multi-criteria evaluation of synthetic biology applications." PloS one 2017; (12)1:e0168564

editing: increase biosecurity, increase biosafety, promote preparedness and development of countermeasures, and promote other benefits to health, environment, and industry.

Working Assumptions: Time Horizon and Intent

Making predictions about the trajectory of emerging technologies is notoriously difficult. Typically, the accuracy of predictions functions in inverse proportion to the length of the time horizon. This study has chosen to examine the risks and benefits of genome editing in the near term (less than five years) and the medium term (5-10 years).

We presume the existence of state and non-state actors with continuous malign intent, and who are searching and probing for ways to exercise this intent. Therefore, we treat malintent as a constant. Similar to numerous other studies, we have employed an in-depth case study approach.[2]

The framework is comprised of four parameters: (1) scenario selection; (2) enabling technology assessment; (3) scenario assessment; (4) governance options. (See box 1.) In what follows, each of the four parameters that comprise the framework are described.

								Governance Options	Option A	Option B
Scenario Selection		**Enabling Technology Assessment**		**Scenario Assessment**				Type (soft, hard, etc.)		
Security relevant governance / policy goal(s)	Example Scenarios	Identify chokepoints and barriers to use	Identify specific genome editing capabilities that are being leveraged	Likelihood of scenario occurring, (low, medium, high)	Consequence (low, medium, high)			**Governance Target**		
								Governance Implementer		
								For each combination of governance goal and governance option: **Feasibility:** **(easy, medium, hard)** **Impact/Effectiveness:** **(more likely, no impact, less likely)**		
Prevent Biosafety Incidents										

[2] Tucker J.B. ed., *Innovation, Dual Use, and Security: Managing the Risks of Emerging Biological and Chemical Technologies*. Cambridge: MIT Press; 2012; U.S. National Academies of Science, *Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct.* Washington, DC: U.S. National Academies of Science; 2016 http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

Prevent Biosecurity Incidents								
Respond to Safety and/or Security Incidents (i.e. Preparedness)								
Promote Other Beneficial Applications								

Table 1. Draft Governance Framework

Scenario Selection

- Identify security relevant policy goals
- Scenario selection

Enabling Technology Assessment

- Identify checkpoints and barriers to use
- Identify specific genome editing capabilities that are being leveraged

Scenario Assessment

- Assess the likelihood of the scenario
- Assess the consequence of the scenario

Governance Assessment

- Identify menu of governance options
- Assess impact, effectiveness, and desirability of governance options for a given scenario
- Assess feasibility of governance options for a given scenario

Box 1. Parameters for Developing and Assessing Governance Options

Scenario Selection

Scenarios to Assist in Grounding Discussions of Security-Relevant Governance Goals and Strategies

In order to ground discussions during the workshop, we have outlined scenarios intended to help illustrate governance goals related to potential (mis)uses of genome editing:

1. Preventing biosafety incidents
2. Preventing biosecurity incidents
3. Responding to biosafety and/or biosecurity incidents (including but not limited to the development of countermeasures)
4. Promoting other beneficial applications (e.g. promoting the bioeconomy)

Each of these goals could themselves be broken down into multiple 'mechanisms of action'

- to prevent ____ experiments from being conducted
- to prevent _____ from falling into the wrong hands
- to enable ____ experiments required for preparedness and other beneficial applications

The scenarios will be distributed at the start of workshop 2. Since their purpose is to serve as a starting point for discussion during workshop 2, they are illustrative "straw people" and not exhaustive. They are also intended to be at a level of abstraction such that the scenarios cover a general category of (mis)use rather than a particular instance. Keeping the scenarios in a middle-ground between abstract and specific is intended to strike a balance between the need for utility, while also being vigilant of potential information hazards.

Parameters for Misuse Scenarios

There are a number of different parameters that will be considered in designing the scenarios. Not all combinations of scenarios will be as likely, and so only a subset will be considered.

Actor and Intent

- No specific malicious intent (but potentially reckless)
    - ✦ Individual (e.g. researcher in academia, industry, or DIY)
    - ✦ Small group (e.g. company or academic lab)
    - ✦ Large concerted program (e.g. national lab)
    - ✦ Intent to create chaos (terrorism)
    - ✦ Transnational non-state actors (e.g. terrorist group)
    - ✦ Domestic terrorists and extremists

- ✦ Lone insiders
- ✦ Lone outsiders

- Intent to target specific individuals or small groups (assassinations)
  - ✦ Individuals
  - ✦ Organized criminals
  - ✦ State based programs

- Intent to target large groups and/or multiple groups (medium or large-scale attack)
  - ✦ Transnational non-state actors (e.g. terrorist group)
  - ✦ Domestic terrorists and extremists
  - ✦ State-based programs

Agent / Mechanism

- Enhanced Agents
  - ✦ Well-known bioweapon agent (pathogen or toxin) modified to be more deadly
- Emerging Agents
  - ✦ Non-traditional bioweapon agent (pathogen or toxin) modified with increased virulence and/or transmissibility
- Advanced Agents
  - ✦ Novel pathogens, toxins, or other types of biological agents (bioregulators) that have been created and engineered to cause death or disability
- Developing vulnerabilities
  - ✦ Vector modified to introduce a vulnerability into an individual (via gene therapy) or population (via gene drive)

Delivery and Dissemination of Biological Agent

- Direct physical introduction
- Infection
- Inheritance (i.e. gene drive)

There are a number of ways in which genome editing could factor into agent development and delivery:

- Exploration/Discovery: Genome editing tools/processes are employed to test/screen/evolve a new function (e.g. dual use research of concern). Note: Exploration/Discovery is likely only feasible for larger groups and/or those with sufficient time, knowledge, and resources.
- Exploit/Deploy: Genome editing tools/processes are employed to exploit a known function.
- Expand/Diffuse: Genome editing is employed to spread a known function (i.e. gene drive).

There are a number of different selection criteria that can be considered:

- Whether the scenario poses a high level of risk or concern
- Whether genome editing tools are likely to change to change the likelihood and/or consequence of a scenario
- Whether genome editing tools are likely to enable a new scenario that was not achievable before
- Whether the scenario was raised in the issue briefs and/or other reports
- Whether the scenario offers a good test case (as part of collection) to illustrate the relative utility of different governance strategies

There are a number of types of activities/processes/products/tools relating to biosafety and biosecurity risk mitigation (i.e. preparedness and response) that could be enabled through uses of genome editing. As we consider the desirability and feasibility of different governance options for preventing misuse of genome editing, it is also important to keep in mind the potential effects of such options on the development of these risk mitigation tools.

- Diagnostics
- Surveillance
- Forensics
- Research Tools (including animal models)
- Medical Countermeasures - Drugs and Vaccines
- Countermeasures - Remediators (e.g. anti-CRISPR, reversal drives)
- Countermeasures - In vivo systems / others (engineering in enhanced immune responses)

There are a number of types of activities/processes/products/tools relating to promoting of benefits through contributions to broad economic and health security. As we consider the desirability and feasibility of different governance options for preventing misuse of genome editing, it is also important to keep in mind the potential effects of such options on the attainment of benefits in these general areas.

- Biomedical Research
- Human Health
- Agriculture
- Industry - Biomanufacturing
- Industry - Tools providers, etc.

Enabling Technology Assessment

The enabling technology assessment is intended to (1) help identify what barriers and choke points exist; and (2) help identify specific genome editing capabilities that are being leveraged and that contribute to the scenario occurring. These include, but not limited to, in the fields of functional genomics, cellular and organism engineering, and gene drives. Different barriers will exist for different users, and they will change over time.[3]

Some common barriers and chokepoints in using genome editing tools include:

Ease of Use

The easier genome editing technology is to use, the more likely it will be used. Factors that impact ease of use include the accessibility of the technology, the level and availability of necessary expertise, and the degree of international diffusion. How easy genome editing technology is to use is also contingent upon the capabilities of the actor in question. In addition, as the technology evolves, the ease of use can change over time.

Accessibility of genome editing technology – Enhanced accessibility to genome editing technologies increase the likelihood of their use. Accessibility includes the ease of acquisition of the required technology, how easy said technology is for an actor to use, and its cost.

Representative questions to consider when assessing accessibility include:

- How easy is it to acquire the necessary hardware, software, and information?
- Is the hardware, software, and information subject to existing governance regimes
- How easy is the required technology to use?
- Is the technology and information commercially available, proprietary, under patent protection, or restricted due to classification?
- How expensive is the technology?
- How dependent is the technology on other upstream or downstream technologies?

Level and availability of necessary expertise – The level and availability of expertise and skills required to use genome editing can present a barrier to its use.

Representative questions to consider when assessing the level and availability of expertise include:

- What type and level of expertise is needed to use the technology?

[3] See Edward J. L. Perello's issue brief, *CRISPR Technology Briefing Note*, for a more detailed discussion of genome editing capabilities, barriers, and points in the CRISPR use process that present potential points of intervention.

- How common is this type and level of expertise?
- If an actor lacks expertise what opportunities are there for her to acquire it?
- How much of the required expertise depends on tacit knowledge?
- How available is this tacit knowledge and how easily transferred is it?
- Are there indicators that the level of expertise required to use the technology is decreasing, i.e., deskilling?

Degree of International Diffusion

The higher the level of international diffusion of genome editing technologies may increase the number of potential actors who may use the technology, both for malicious and beneficial use.

Representative questions to consider include:

- How many international sources of the technology are there?
- How easy is it to transfer the technology across national borders?
- Are there local sources available to acquire the technology?

Maturity and Rate of Advance

The maturity of a technology can help determine existing barriers and may aid in identifying how barriers and bottlenecks may be overcome in the future. The rate at which techniques and technologies associated with genome editing advance is closely related to the maturity of the technology.

Representative questions to consider include:

- How quickly is the technology advancing in terms of reliability, speed, throughput, accuracy, or cost?
- Is the rate of advance linear, exponential, incremental, or declining?
- Where does the technology lie on the development pipeline ranging from basic research to applied research to advanced development to commercialization?

Convergence

The degree to which particular uses of genome editing technology requires convergence between multiple scientific disciplines may pose a barrier to use.

Representative questions to consider include:

- What other technologies and fields aid the use of genome editing?

- Is the maturity and rate of advance of genome editing dependent or driven further by contributions from other disciplines?

Scenario Assessment

The scenario assessment, divided into two parts, is intended to first, help identify how genome editing changes the likelihood of the given scenario (e.g., more likely, no impact, less likely) occurring, and second help estimate the consequences should it occur.

The information gathered in the enabling technology assessment can help inform our conclusions about the likelihood of the scenario coming to being. Such information may include details about an increased number of possible actors who are able to bring the scenario to fruition due to lowered barriers or widened/overcome choke points (e.g., easier to use technology, more common skills that are easily acquired, more available resources, cheaper and less sophisticated lab/equipment). In addition, there may be information that points to the possibility that those actors who already have the skills, equipment and knowledge are now enabled to exercise their intent more easily and with greater frequency.

Identify and describe the potential consequences and their magnitude should the scenario occur. Some common metrics for consequences include:

- The number of human deaths and injuries
- Direct and indirect economic costs
- Psychosocial impacts
- Impact on environment and biodiversity
- Human lives saved or improved
- Direct and indirect economic benefits

Governance Options for Genome Editing: Lessons from Biosafety and Biosecurity

Governance measures to prevent biotechnology from causing harm have generally had two broad purposes:

- **Safety**: Preventing the accidental infection of laboratory workers and the release of dangerous pathogens into the environment
- **Security**: Preventing the unauthorized access, theft, loss, or misuse of dangerous pathogens, technology, knowledge, or expertise to cause harm

In the United States, governance measures designed to achieve each of these objectives have evolved mostly in parallel. There has been limited cross-over between these domains, primarily for bureaucratic reasons. At times, however, concerns in one domain have impacted the other. For

example, the debate over "gain of function" experiments shifted from early concerns about biosecurity to a strong emphasis on biosafety after several close-calls with mishandled pathogens at elite biomedical research centers.

Since the emergence of recombinant DNA technology in the early 1970s, a range of different governance approaches have been applied to emerging biotechnologies. The relevant policies governing the safe, secure, and responsible conduct of life sciences research are found in multiple locations which span the continuum from codes of conduct and standards to guidelines to regulations to legislation. It is worth stepping back to think about the governance measures developed for biosafety and biosecurity purposes along several dimensions to inform our thinking on how to adapt them to the new challenges posed by genome editing: institutionalization, anticipation, adaptiveness, and comprehensiveness.

One way to compare these governance approaches is the degree to which they are institutionalized, meaning the degree to which there are organizations equipped with the authority, information, and expertise to review the performance and activities of the entities being supervised and enforce compliance. The Government Accountability Office (GAO) has identified five key elements of effective oversight in areas where low-probability events can have high negative consequences:[4]

- **Independence**: The organization conducting oversight should be structurally distinct and separate from the entities it oversees.
- **Ability to perform reviews**: The organization should have the access and working knowledge necessary to review compliance with requirements.
- **Technical expertise**: The organization should have sufficient staff with the expertise to perform sound safety and security assessments.
- **Transparency**: The organization should provide access to key information, as applicable, to those most affected by operations.
- **Enforcement authority**: The organization should have clear and sufficient authority to require that entities achieve compliance with requirements

Based on these parameters, governance options can be sorted into three categories that reflect their degree of institutionalization:

- **High**: Compliance is mandatory for all entities based on legal and regulatory authorities and an organization has been assigned responsibility for implementation. The implementing organization has the capacity to assess compliance through inspection and/or audit and has the authority to impose penalties for non-compliance.
- **Medium**: Entities agree to comply voluntarily with standards or guidance issued by an implementing organization. Institutions are responsible for creating their own internal processes and procedures to ensure compliance. The implementing organization has little, or no, authority and/or capacity to assess compliance on a routine basis or impose penalties for non-compliance.

[4] Government Accountability Office (GAO), High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens, GAO-18-145. Washington, DC: GAO; October 17, 2017.

- **Low**: Compliance is voluntary, there are no widely agreed-upon standards for what constitutes compliance, there is no mechanism for assessing compliance, and there are no penalties for non-compliance.

Governance measures that have been applied to biotechnology can be arrayed along a spectrum from the most stringent, which are typically embodied in legislation and are highly institutionalized, to the least stringent, which are informal measures that rely on voluntary compliance by stakeholders (see Table 1). This typology is illustrative, not exhaustive. In addition, the boundaries between these categories are fluid and the degree of institutionalization within each category can also vary.

High	Medium	Low
International Treaty	Safety Guidelines	Codes of Conduct
Criminal Statute	Security Guidelines	Education and Awareness-Raising
Statutory Regulations	Industry Self-Governance	Pre-Publication Review
Mandatory Licensing, Certification, Registration	Scientific Community Self-Governance	Transparency Measures
Export Controls	Adoption of International Standards	
Reporting Requirements	Pre-Publication Review	
Research Proposal Review		
Funding Review		

Table 2. Typology of Biotechnology Governance Measures Based on Degree of Institutionalization[5]

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 changes.[6] This reactive model of policy-making, however, is widely viewed as being unsuited for an era of rapid technological change. In addition to the degree of institutionalization, it is also worth considering three other dimensions of governance measures: anticipation, adaptability, and comprehensiveness. Is the governance measure narrowly tailored and rigid, which would make it difficult to adapt to changing circumstances, or does it have a broad scope and is flexible enough to make it easy to revise? Finally, these governance measures can vary in their scope or comprehensiveness ranging from being mandatory for all individuals and institutions, regardless

[5] This table is adapted from Figure 2.1 in Tucker J.B. "Review of the Literature on Dual-Use," in Jonathan B. Tucker, ed., *Innovation, Dual Use, and Security.* Cambridge: MIT Press; 2012: p. 34.

[6] On the role of focusing events in revolutionary policy changes, see Birkland T.A. *After disaster: Agenda setting, public policy, and focusing events*. Washington, DC: Georgetown University Press; 1997; and Birkland T.A. *Lessons of Disaster: Policy Change after Catastrophic Events*. Washington, DC: Georgetown University Press; 2007. On the theory of punctuated equilibrium in evolutionary biology, see Gould S.J. *Punctuated Equilibrium*. Cambridge, MA: Harvard University Press; 2007.

of source of funding to being required for all institutions that receive Federal funding to being voluntary for all individuals and institutions.

Examples of Current Biosafety and Biosecurity Governance Measures

This section provides a brief summary of an existing biotechnology governance measure from each of these three categories. The following section explores how these different types of governance measures could be applied to genome editing. While this section is grounded in actual policy and practice, the second part of this exercise is necessarily speculative.

Example from Biosecurity: High Degree of Institutionalization

The epitome of a highly institutionalized governance measure in the domains of biosafety and biosecurity is the Federal Select Agent Program (FSAP). Following the terrorist attacks on September 11 and the Amerithrax attack during the fall of 2001, laboratory biosecurity measures were strengthened dramatically. Congress passed the USA PATRIOT ACT in 2001 and the Public Health Security and Bioterrorism Preparedness and Response Act (Public Law 107–188, June 12, 2002) in 2002. Together, these new measures were intended to prevent unauthorized access to a list of designated pathogens and toxins (called select agents) by requiring labs that possessed these agents to register with the Centers for Disease Control and Prevention (CDC) (for human pathogens) and/or the Animal Plant Health Inspection Service (APHIS) (for plant and animal pathogens), institute inventory and accounting measures, put in place controls to prevent unauthorized access to the select agents, provide access to these materials only to those who passed a background check administered by the Department of Justice, and submit to inspections and audits by CDC and/or APHIS to ensure that these regulations are being followed. All institutions working with select agents are required to designate a Responsible Official (RO) to be responsible for implementing the regulations. Following revelations in 2008 about the role of Bruce Ivins, an Army biodefense researcher, as the perpetrator of the Amerithrax attacks, new biosecurity measures were established focused on preventing insider threats such as personnel reliability programs to provide continuous monitoring of personnel granted access to Select Agents. At the same time, the FSAP was optimized to better balance the costs and benefits of these enhanced biosecurity measures. A subset of 15 select agents were designated as Tier 1 agents, a category of pathogens and toxins that present the greatest risk of deliberate misuse. These Tier 1 select agents are subject to even more stringent security measures including personnel reliability programs and enhanced physical and cyber security controls.

The mandate of FSAP extends into the domain of biosafety as well. Labs that work with Select Agents are required to comply with the biosafety standards described in the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual. BMBL classifies pathogens and toxins into different risk groups with corresponding biosafety levels, codifies codes of practice for each biosafety level, and serves as the authoritative text on the safety hazards posed by infectious microorganisms. The CDC and APHIS are empowered to assess whether labs are complying with these biosafety standards and to levy penalties if they are not. The Select Agent regulations also specify reporting requirements for the theft, loss, or release (including occupational exposure or release of an agent or toxin from a laboratory) of select agents. In addition, researchers who want to engineer drug resistance or toxin production into a select agent have to receive the approval of the NIH as well as the secretary of HHS or USDA (depending on which select agent is involved).

This decision is based solely on whether the research can be conducted safely and securely, not whether the research poses dual-use research concerns.

Example from Biosafety: Medium Degree of Institutionalization

The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids (called the NIH Guidelines) are characterized by a medium level of institutionalization. The NIH Guidelines govern the safety of certain types of experiments with different degrees of oversight depending on the type of experiment. The NIH Guidelines are written by the Recombinant DNA Advisory Committee (RAC). Institutional Biosafety Committees (IBCs) 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. At least two members must be from the community and not be affiliated with the institution. 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. Protocols for the transfer of recombinant or synthetic DNA into human research participants must be registered with the NIH, and OBA will determine if the protocol requires approval by the RAC. IBCs are also responsible for monitoring the conduct of human gene therapy research and must report any serious adverse events to both the NIH and Food and Drug Administration (FDA). Experiments that involve the cloning of highly toxic toxins requires the approval by the Office of Science Policy that oversees OBA and the transfer of drug resistance traits requires approval by both the RAC and the director of the NIH. If recombinant material is to be released into the environment, then the Environmental Protection Agency (EPA) would be involved.

The NIH Guidelines specify reporting requirements for significant problems, violations, and research-related accidents and illnesses. Compliance with the NIH Guidelines is required for institutions that receive funding from NIH. Non-compliance with the NIH Guidelines can lead to the loss of NIH funding. In addition, 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 of experiments that potentially fall under the purview of the guidelines.

The safety of research with rDNA and synthetic nucleic acids relies on a long-standing system of oversight that uses a tiered approach with primary responsibility for review being conducted at the local level by IBCs, and the RAC conducting review upon request and for "restricted experiments." One weakness in this system is a lack of independence at the local and Federal levels, since the IBC is reviewing research conducted by PIs at its own institution and the RAC is part of NIH which is typically the agency that funds the research being reviewed. Another weakness is that the NIH 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.[7] Another longitudinal study found improved compliance rates among IBCs due to greater outreach by NIH and adverse media attention.[8] 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. At the same time, this study concluded that "there may be many IBCs that lack adequate staffing and oversight, and that do not provide the required training."[9] Finally, although NIH has the power to terminate funding for violation of the Guidelines, it has never done so. A final weakness of biosafety oversight is that it is completely voluntary for institutions, such as pharmaceutical and biotech companies, that do not receive NIH funding. 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.

The NIH Guidelines have displayed a high degree of adaptation. First promulgated in 1976, the guidelines originally prohibited six types of rDNA experiments due to biosafety concerns: the transfer of drug resistance traits, genes for the biosynthesis of dangerous toxins, increasing the virulence or host range of a pathogen, the release of a recombinant organism into the environment, and experiments requiring large-scale production (10 liters or more) of a recombinant organism. As researchers gained more experience with these types of experiments and recombinant organisms, these prohibitions were eventually lifted. The NIH Guidelines underwent a major revision in 1978 and were then modified roughly every three months for several years.[10] The RAC had three important features. First, it was housed in NIH, which is not a regulatory body; therefore, adherence to its guidelines was strictly voluntary (although compliance was a condition of funding from NIH). Second, this type of oversight provided much more flexibility for amending the guidelines compared to traditional regulations. Indeed, the guidelines were amended regularly to account for scientific developments, most of which demonstrated that the safety hazards posed by rDNA research was less than initially expected and therefore certain types of restrictions could be eased or lifted.[11] Third, the RAC was initially composed entirely of scientists and has remained dominated by scientists on the premise that they have the expertise needed to assess the benefits and risks of research and devise precautions that can reduce risks while not unduly impeding scientific progress.

Examples from Dual-Use Research: High and Medium Degrees of Institutionalization

In 2014, the U.S. government issued a policy to govern dual-use research of concern (DURC) 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,

[7] Sunshine Project, *Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research*. Austin, TX: Sunshine Project; October 2004; and Race M.S. and Hammond E. "An Evaluation of the Role and Effectiveness of Institutional Biosafety Committees in Providing Oversight and Security at Biocontainment Laboratories," *Biosecurity and Bioterrorism* 2008; 6(1): pp. 19-35.
[8] Hackney R.W. Jr., Myatt T.A., Gilbert K.M., Caruso R.R., and Simon S.L. "Current Trends in Institutional Biosafety Committee Practices," *Applied Biosafety* 2012; 17(1): p. 11-18.
[9] Ibid.
[10] Talbot B. "Development of the National Institutes of Health Guidelines for Recombinant DNA Research," *Public Health Reports* 1963; 96(4): p. 361.
[11] The rDNA Guidelines have been amended 26 times since 1994. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html

animals, the environment, materiel, or national security." The scope of DURC subject to oversight, however, was narrowed to seven types of experiments (based on those first put forward by the Fink Committee in 2004) conducted on one of the 15 Tier 1 select agents or toxins. This policy only applied to public or private research institutions that received Federal funding for life science research, even if the DURC was not being conducted with government funding. This policy also applies to foreign research institutions that receive U.S. funding for DURC research. Institutions that receive Federal funding for life sciences research are required to establish an Institutional Review Entity (IRE) to implement the DURC policy.

Examples from Synthetic Biology: Medium and Low Degrees of Institutionalization

The field of synthetic biology is characterized by a mix of governance measures that rank low and medium in terms of institutionalization. In 2009, a group of leading DNA synthesis firms formed the International Gene Synthesis Consortium (IGSC) announced that they were voluntarily adopting customer and sequence screening standards.[12] 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 order sequence and a regulated agent, the order and the customer are scrutinized manually.[13] 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, and the company can contact government authorities. The members of the IGSC share information on a regular basis within the confines imposed by need to safeguard proprietary business information. Implementation of the IGSC's standards are up to 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. Still, the IGSC currently accounts for 80% of the global market in DNA synthesis.[14]

In parallel with the industry's development of codes of conduct, the United States government's Department of Health and Human Services (HHS) crafted voluntary guidelines for US-based DNA synthesis providers that were published in 2010. These guidelines details customer screening measures, standards for sequence screening, and the process for raising concerns with the appropriate government authorities. These standards only cover double-stranded DNA longer than 200 base pairs; they do not cover short strings of nucleotides called oligos.[15] However, there is no mechanism for assessing whether companies, based in the United States or elsewhere, are in compliance with the HHS guidance.

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[12] Tucker J.B. "Double-Edged DNA: Preventing the Misuse of Gene Synthesis," *Issues in Science and Technologty* Spring 2010.
[13] Hanselman DS. "Tools and opportunities to enhance risk analysis." Powerpoint slides presented at: *National Academies of Sciences, Engineering and Medicine Committee on Future Biotechnology Products and Opportunities to Enhance the Capabilities of the Biotechnology Regulatory System* 2016 June 2; Washington, DC; and Carter SR, Friedman RM. *DNA synthesis and biosecurity: lessons learned and options for the future*. La Jolla, CA: J. Craig Venter Institute; 2015; and IGSC, "Harmonized Screening Protocol© v2.0," 19 November 2017, https://genesynthesisconsortium.org/wp-content/uploads/IGSCHarmonizedProtocol11-21-17.pdf
[14] International Gene Synthesis Consortium. The promotion of biosecurity. IGSC website. http://www.genesynthesisconsortium.org.
[15] Department of Health and Human Services. Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA. Washington, DC: Department of Health and Human Services; 2010.

Potential Governance Options for Genome Editing

Based on previous experience with biosafety and biosecurity governance, this section explores some governance options for genome editing. The following descriptions of governance measures as applied to genome editing are for illustrative purposes and are designed to stimulate discussion. They are intended primarily to illustrate how the same option can be implemented in different ways based on how institutionalized the governance measure is. They do not reflect an endorsement by the project team or any participants in the workshop.

Pre-Registering Gene Drive Research

Kevin Esvelt has proposed that scientists working on gene drives pre-register their research: "Ideally, researchers would formally preregister new projects by publishing a preprint describing their rationale and planned experimental approach."[16] This governance approach would use transparency to promote collective awareness of planned research and facilitate assessments of the risks of such research by a multidisciplinary community. It is possible to imagine implementing this governance measure in ways that range in the degree of institutionalization from low to high.

At the high end of the spectrum, a regulatory agency, such as EPA, FDA, or USDA, could assert its jurisdiction over this type of research.[17] The agency could require research on gene drives to be registered as part of its regulatory approval process for products based on this technology. One such example of this model is ClinicalTrials.gov, which was mandated by legislation. NIH and FDA established the website to register clinical trials for investigational new drugs developed using public or private funding. The FDA has the authority to impose penalties on entities that fail to register trials on the website.

At the medium end of the spectrum, a funding agency, such as NIH, could require that researchers working on gene drives register their planned experiments on a publicly available website maintained by the agency as a condition of funding. If narrowly tailored, this approach would only capture scientists who receive funding from NIH (or possibly any Federal source). By requiring institutions that receive NIH or Federal funding for life sciences research register such experiments, regardless of the source of funding for the actual experiment, this approach could cover a wider scope. This approach, however, would not cover research conducted by institutions, such as corporations, that do not receive NIH or Federal research funding. Compliance with this requirement would be left largely to the scientific community to police itself, with blatant violations being easily detected when scientists publish articles based on unregistered research.

At the low end of the spectrum, a group of scientists, an international organization, or non-governmental organization (NGO) could establish a website where scientists could voluntarily register information about planned and ongoing research with gene drives. The information to be included on the website would be determined by the gene drive research community, or a subset of it, submission of information would be completely voluntary, there would be no formal mechanisms for assessing compliance, and no penalties for not participating in the registry.

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[16] Esvelt K.M. "Precaution: Open Gene Drive Research." *Science* 2017; 355(6325): pp. 589–590. doi:10.1126/science.aal5325.

[17] It has been pointed out that several agencies, including the FDA, USDA, and EPA, may have overlapping authorities for regulating gene drives. For our purposes, the identity of the specific agency is not important. Oye, K.A., Esvelt K., Appleton E., Catteruccia F., Church G., Kuiken T., Lightfoot S.B.Y., McNamara J., Smidler A., and Collins J.P. "Regulating Gene Drives." *Science* 2014; 345(6197): pp. 626–628. doi:10.1126/ science.1254287.

Moratorium

Several different parties have proposed moratorium for different genome editing applications. A coalition of environmental groups lobbied a 2016 meeting of the UN Convention on Biodiversity (CBD) to call for a moratorium on gene drives. This proposal was resisted by scientists and rejected by governments, but is likely to resurface at the CBD's next meeting in 2018.[18] In April 2015, another group of prominent scientists called for a global moratorium on "any attempts at germline genome modification for clinical application in humans."[19] This call for a moratorium was not picked up by the broader scientific community. In December 2015, an international summit on human gene editing issued a statement of principles that listed conditions under which germline editing for clinical purposes could be pursued.[20] Research on germline editing of embryos, initially on non-viable but now with viable embryos, has proceeded apace. In 2017, researchers in China, the United States, and the United Kingdom used CRISPR to modify the germline of viable embryos. Nonetheless, moratoriums have been used in the past both at the early "discovery" phase of science and during the "exploration" phase of research.

At the highest end of the governance spectrum, a government could criminalize certain research, such as the development of biological weapons or the synthesis of the variola virus. A government could also impose a moratorium on research with a new biotechnology by cutting off funding for it. In 2001, the Bush Administration tightly restricted the types of stem cell research that could be conducted with Federal funding. In 2014, the White House ordered a moratorium on Federally-funded research with influenza, SARS and MERS that involved "gain of function" experiments for safety reasons. At the low end of the spectrum, scientists could collectively decide to pause certain types of experiments or research until safety, security, ethical or other issues were resolved. In 1974, a National Academies of Science committee called for an unprecedented voluntary moratorium on certain types of rDNA experiments until there were safeguards in place to ensure that such research could be conducted safely.[21] Likewise, in January 2012, in the wake of controversy over a pair of experiments that demonstrated that avian influenza could be transmitted between mammals, the influenza community instituted a voluntary moratorium on these "gain of function" experiments.[22]

Appendix: Evolution and Evaluation of the Safety and Security Regimes Governing Biotechnology

Governance measures to prevent biotechnology from causing harm have generally had two broad purposes:

[18] Callaway E. "'Gene Drive' moratorium shot down at UN biodiversity meeting," *Nature News* 2016: p. 1.
[19] Baltimore D., *et al.*, "A prudent path forward for genomic engineering and germline gene modification," *Science* 2015; 348 (6230): p. 36-38. DOI: 10.1126/science.aab1028.
[20] "On Human Gene Editing: International Summit Statement by the Organizing Committee," *in International Summit on Human Gene Editing: A Global Discussion*. Washington, DC: National Academies Press; 2015 December 3.
[21] Frederickson D.S. "Asilomar and Recombinant DNA: The End of the Beginning," in Kathi E. Hanna, ed., *Biomedical Politics*. Washington, DC: National Academies Press; 1991: pp. 258-298.
[22] Fouchier R.A.M., García-Sastre A., Kawaoka Y., *et al.*, "Pause on avian flu transmission studies," *Nature* 2012; 481: pp. 443.

- **Safety**: Preventing the accidental infection of laboratory workers and the release of dangerous pathogens into the environment
- **Security**: Preventing the unauthorized access, theft, loss, or misuse of dangerous pathogens, technology, knowledge, or expertise to cause harm

In the United States[23], governance measures designed to achieve each of these objectives have evolved mostly in parallel. There has been limited cross-over between these domains, primarily for bureaucratic reasons. At times, however, concerns in one domain have impacted the other. For example, the debate over "gain of function" experiments shifted from concerns about biosecurity early on to a strong emphasis on biosafety after several close-calls with mishandled pathogens at the CDC, NIH, and Dugway Proving Ground.

Biosafety

When recombinant DNA (rDNA) technology first emerged in the early 1970s, safety concerns were the primary risks associated with the technology. Leading scientists in the field of molecular biology called attention to these risks and called for the National Academy of Sciences (NAS) to review potential hazards associated with recombinant DNA and recommend actions to mitigate those hazards. The NAS committee called for an unprecedented voluntary moratorium on rDNA experiments that could result in the introduction of antibiotic resistance or toxin formation, or experiments where DNA from oncogenic viruses was put into plasmids or viral vectors. In addition, it was recommended that other rDNA experiments only be undertaken after very careful consideration until more was known about their safety. The committee also requested that the director of the NIH consider establishing an advisory committee focused on recombinant DNA and that an international meeting of scientists be convened to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules. In February 1975, an international group of scientists convened at the Asilomar Conference Center in California. The group explicitly excluded the risks that rDNA could be used for biological warfare purposes and instead focused on potential safety hazards. In light of the degree of public concerns about safety, uncertainties associated with the risks posed by this research, and the potential for huge benefits to biological research and for biomedical applications, the group called for rDNA experiments to continue but under strict guidelines.[24]

In response, the NIH established the Recombinant DNA Advisory Committee (RAC) to craft the guidelines to govern research in this growing field. In 1976 NIH published the first Guidelines for Research Involving Recombinant DNA Molecules (called the NIH Guidelines). The NIH Guidelines describe in detail the microbiological practices, equipment, and facility safeguards that correspond to the four ascending levels of physical containment and established criteria for assigning rDNA experiments to a containment level based on an assessment of the potential hazards of the experiment. The original guidelines prohibited six types of rDNA experiments due to biosafety concerns: the transfer of drug resistance traits, genes for the biosynthesis of dangerous toxins, increasing the virulence or host range of a pathogen, the release of a recombinant organism

[23] This section only covers biosafety and biosecurity policies in the United States. A future version of this section will include a section at the end on international policies in these domains.
[24] Frederickson D.S. "Asilomar and Recombinant DNA: The End of the Beginning," in Kathi E. Hanna, ed., *Biomedical Politics*. Washington, DC: National Academies Press; 1991: pp. 258-298.

into the environment, and experiments requiring large-scale production (10 liters or more) of a recombinant organism. As researchers gained more experience with rDNA technology, these prohibitions were gradually loosened until the RAC eliminated them entirely in 1982. In 2012, NIH updated the guidelines, following a recommendation made by National Science Advisory Board for Biosecurity (NSABB), to specify that the use of synthetic nucleic acids in basic and clinical research were covered by the guidelines.

Institutional Biosafety Committees (IBCs) are the first line of review for research with recombinant and synthetic DNA. All NIH-funded institutions are required to have an IBC which is composed of at least five members who have expertise in the fields of recombinant and synthetic DNA. At least two members must be from the community and not be affiliated with the institution. Institutions that engage in large-scale experimentation with recombinant or synthetic organisms or operate BSL-3 or BSL-3 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. Protocols for the transfer of recombinant or synthetic DNA into human research participants must be registered with the NIH, and OBA will determine if the protocol requires approval by the RAC. IBCs are are also responsible for monitoring the conduct of human gene therapy research and must report any serious adverse events to both the NIH and Food and Drug Administration (FDA). Experiments that involve the cloning of highly toxic toxins requires the approval by the Office of Science Policy that oversees OBA and the transfer of drug resistance traits requires approval by both the RAC and the director of the NIH. If recombinant material is to be released into the environment, then the Environmental Protection Agency (EPA) would be involved.

The NIH Guidelines specify reporting requirements for significant problems, violations, and research-related accidents and illnesses. Compliance with the NIH Guidelines is required for institutions that receive funding from NIH. Non-compliance with the NIH Guidelines can lead to the loss of NIH funding. In addition, 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 of experiments that potentially fall under the purview of the guidelines.

At roughly the same time that molecular biologists were grappling with the safety risks posed by a new technology, infectious disease researchers were formalizing best practices for reducing the well-known risks to laboratory workers conducting research on naturally occurring pathogens. In 1974, the Centers for Disease Control (CDC) published *Classification of Etiologic Agents on the Basis of Hazard* which introduced the concept of ascending levels of containment that corresponded to risks associated with handling infectious microorganisms. In 1984, a multi-year, collaborative effort led by the CDC and NIH culminated in the publication of the first edition of the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual. BMBL refined the classification of pathogens and toxins into different risk groups with corresponding biosafety levels, codified codes of practice for each biosafety level, and began serving as the authoritative text on the safety hazards posed by infectious microorganisms. The recommended practices, safety equipment, and facility safeguards described in the BMBL are advisory in most circumstances and are designed to empower members of the laboratory community with the knowledge they need to

protect themselves, the public and the environment.[25] The BMBL uses performance-based guidelines that rely on the self-interest and scientific judgement of principal investigators (PIs) to conduct a risk assessment and adopt appropriate precautions.[26] The advisory nature of the BMBL provides researchers with flexibility to adopt different approaches to achieving the safety goals described in the manual. The BMBL is not a regulatory document with prescriptive rules that specify how researchers are supposed to implement it.[27] Adherence to the BMBL, however, is generally required by BSL-3 and 4 laboratories constructed with NIH funding or that receive NIH funding for their research. At the same time, NIH does not have the authority or means to verify compliance with the BMBL or punish violations. In addition, the CDC and U.S. Department of Agriculture (USDA) requires labs that work with Select Agents to comply with the BMBL and these agencies are empowered to enforce this requirement.

The only Federal regulations that apply to safety in laboratory setting are Occupational Health and Safety (OSHA) regulations on bloodborne pathogens and the use of personal protective equipment (PPE). Federal research grants require compliance with these OSHA regulations as a condition for funding. There are no federal OSHA regulations, however, that specifically address worker protection from contact-, droplet- and airborne-transmissible infectious agents.[28]

Biosecurity

In the mid-1990s, concerns about bioterrorism led to the first biosecurity regulations. The combination of the Aum Shinrikyo sarin attack on the Tokyo subway system in March 1995, the Oklahoma City bombing in April 1995, and the attempt by white supremacist Larry Wayne Harris to order Yersinia pestis through the mail in May led to the first security regulations on civilian biological research in the United States. In 1997, the CDC began implementing the Antiterrorism and Effective Death Penalty Act of 1996 (Public Law 104–132, April 24, 1996) designed to regulate the transfer of 36 select agents and toxins deemed to have the potential to pose a severe threat to public health and safety. To ensure that the transfer of these agents was carried out only by and between responsible parties, CDC required that laboratories transferring these select agents be registered and report each transfer to the CDC.

Following the terrorist attacks on September 11 and the Amerithrax attack during the fall of 2001, laboratory biosecurity measures were strengthened dramatically. In 2001, Congress passed the USA PATRIOT ACT and in 2002, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107–188, June 12, 2002). Together, these new measures were intended to prevent unauthorized access to an expanded list of designated pathogens and toxins, including requiring labs possessing these agents to register with CDC (for human pathogens) and/or Animal Plant Health Inspection Service (APHIS) (for plant and animal pathogens), institute inventory and accounting measures, put in place controls to prevent unauthorized access to the

[25] Center for Disease Control (CDC). *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*: pp. 1-8. https://www.cdc.gov/biosafety/publications/bmbl5/bmbl5_sect_i.pdf

[26] Wilson D.E. "Where are we now and where are we going?" *Revision of the Biosafety and Microbiological and Biomedical Laboratories (BMBL)*. Office of Research Services: National Institutes of Health; 2017. https://osp.od.nih.gov/wp-content/uploads/Session_III_Talk_Wilson.pdf

[27] National Academies of Sciences, Engineering, and Medicine (NASEM). Soliciting Stakeholder Input for a Revision of Biosafety in Microbiological and Biomedical Laboratories (BMBL): Proceedings of a Workshop 2016; https://www.nap.edu/read/23585/chapter/3.

[28] OSHA developing an infectious disease rule to protect workers from those risks. See, Nerad T.A. "OSHA Regulations and Guidance Applicable to Laboratories: What's Current and What's in Development?" *Occupational Safety and Health Administration* 2017; https://osp.od.nih.gov/wp-content/uploads/Session_III_Talk_Nerad.pdf.

select agents, provide access to these materials only to those who passed a background check administered by the Department of Justice, and prohibit access to any biological agents by "restricted persons." Institutions working with Select Agents were required to designate a Responsible Official (RO) to be responsible for implementing the regulations. The Select Agent regulations also specify reporting requirements for the theft, loss, or release (including occupational exposure or release of an agent or toxin from a laboratory) of a select agent or toxin.

In addition, since 2002, researchers who want to conduct so-called "restricted experiments" listed under the NH rDNA Guidelines (that involve engineering drug resistance or toxin production into a select agent) have to receive the approval of the NIH as well as the secretary of HHS or USDA (depending on which select agent is involved). In general, NIH defers to FSAP on requests to conduct a restricted experiment with a select agent. This decision is based solely on whether the research can be conducted safely and securely. The question of whether the results might be considered dual-use research of concern is beyond the scope of the FSAP. In addition, it is worth noting that FSAP does not regulate the information produced by select agent and toxin experiments.[29] Between 2006 and 2014, 91 restricted experiments were proposed to HHS with 31 being approved.[30]

Following revelations in 2008 about the role of Bruce Ivins, an Army biodefense researchers, as the perpetrator of the Amerithrax attacks, new biosecurity measures were established focused on preventing insider threats such as personnel reliability programs to provide continuous monitoring of personnel granted access to Select Agents. At the same time, the Select Agent program was optimized to better balance the costs and benefits of these enhanced biosecurity measures. In 2010, Executive Order 13546 declared a subset of Select Agents to be Tier 1 agents, a category of pathogens that present the greatest risk of deliberate misuse with the greatest potential to cause mass casualties or other devastating effects. In 2012, CDC and APHIS finalized the new Select Agent Regulations which imposed new security measures, including personnel reliability programs and enhanced physical and cyber security controls, on the Tier 1 agents.

At the same time that laboratory biosecurity was receiving increased attention due to the September 11th terrorist attacks and the anthrax letters, experiments that demonstrated the ability of scientists to modify pathogens to be more virulent or overcome medical countermeasures led to heightened concerns about dual-use research in the life sciences. For the first decade, efforts to govern dual-use research focused on defining the scope of the problem, educating scientists about the nature of the problem, and debating different proposals for how to provide effective oversight. The National Academy of Sciences played an important role in this process. The 2004 Fink report had a lasting impact on this domain by defining seven categories of experiments that posed dual-use risks and calling for a national dual-use research oversight system.[31] The Fink report led directly to the creation of the National Science Advisory Board for Biosecurity (NSABB) under

[29] Edwin S.S. and Isaac F.E. "Federal Select Agent Program Perspective: Intersection of the NIH Guidelines with the Select Agent Regulations," *NIH Guidelines: Honoring the Part, Charting the Future* 2017; https://osp.od.nih.gov/wp-content/uploads/Session_III_Talk_Edwin.pdf.

[30] Smith J., Gangadharan D., and Weyant R. "Review of Restricted Experiment Requests, Division of Select Agents and Toxins, Centers for Disease Control and Prevention, 2006-2013," *Health Security* 2015; 13(5): pp. 307-316.

[31] The categories are: demonstrating how to render a vaccine ineffective, conferring resistance to therapeutically useful antibiotics or antiviral agents, enhancing the virulence of a pathogen or rendering a non-pathogen virulent, increasing the transmissibility of a pathogen, altering the host range of a pathogen, enabling the evasion of diagnostic/detection modalities, and enabling the weaponization (enhanced ability to be disseminated as a respirable aerosol) of a biological agent or toxin.

NIH, which began the process of developing such an oversight system. NSABB published its proposal for a national dual-use research oversight system in 2007, but the proposal was not acted upon for several years.[32] In the meantime, the CDC and NIH instituted their own programs to review intramural research projects for dual-use concerns.[33]

Within the domain of dual-use research in the life sciences, one area that has received special attention was synthetic biology. In 2002, the synthesis of poliovirus raised concerns about the ability of this technology to create pathogens from scratch thereby circumventing the Select Agent regulations. In 2005, the reconstruction of the 1918 influenza virus raised fears about the accidental or intentional release of a virus capable of causing a pandemic. NSABB reviewed the manuscripts associated with this experiment and unanimously agreed that they could be published. As a result of this experiment, HHS added 1918 influenza virus to the list of Select Agents--the first time a product of synthetic biology was subject to security regulations. In 2009, two groups of leading DNA synthesis firms, the International Gene Synthesis Consortium (IGSC) and the International Association of Synthetic Biology (IASB), announced that they were voluntarily adopting customer and sequence screening standards.[34] Although IASB is now defunct, IGSC has grown into an international association that accounts for 80% of the global market in DNA synthesis.[35] In parallel with the industry's development of codes of conduct, the United States crafted voluntary guidelines for US-based DNA synthesis providers that were published in 2010. These guidelines details customer screening measures, standards for sequence screening, and the process for raising concerns with the appropriate government authorities. [36]There is no mechanism for assessing whether U.S. companies are in compliance with the HHS guidance.

Dual-use research oversight faced a major inflection point in 2011 when Ron Fouchier from the Netherlands and Yoshihiro Kawaoka in the United States submitted a pair of manuscripts that described how to generate strains of H5N1 avian influenza that were transmissible between mammals. By not only demonstrating that mammalian transmission of the virus was possible, but also providing information on how to construct such a virus, these experiments triggered a broader concern with the safety and security of so-called "gain of function" experiments. "Gain of function" experiments were defined as experiments that resulted in the creation of so-called potential pandemic pathogens with enhanced virulence and/or transmissibility. In November 2011, NSABB recommended that sensitive information be removed from the manuscripts before publication--the first time they had made such a recommendation. In January, Fouchier, Kawaoka, and 37 other influenza researchers agreed to a 60-day moratorium on research with strains of H5N1 with heightened transmissibility.[37] In February 2012, after hearing presentations from Fouchier and Kawaoka, a WHO advisory group approved the full publication of both manuscripts. In

[32] Epstein G.L. "Preventing Biological Weapon Development Through the Governance of Life Science Research," *Biosecurity and Bioterrorism* 2012; 10(1): pp. 17-37.
[33] Centers for Disease Control and Prevention, *Oversight and Clearance of Dual-Use Research of Concern, CDSM-2007-01* 2007 March 23; and Sttitt-Fischer M.S. "The National Institute of Health Dual-Use Screening Program: A Proposed Quality Control Model," *53rd Annual Biological Safety Conference* 2010 October 5.
[34] Tucker J.B. "Double-Edged DNA: Preventing the Misuse of Gene Synthesis," *Issues in Science and Technology* Spring 2010.
[35] International Gene Synthesis Consortium. *The promotion of biosecurity*. IGSC website. http://www.genesynthesisconsortium.org.
[36] US Department of Health and Human Services. *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA*. Washington, DC: US Department of Health and Human Services; 2010. https://www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf.
[37] Fouchier R.A.M., García-Sastre A., Kawaoka Y., *et al*., "Pause on avian flu transmission studies," *Nature* 2012; 481: p. 443.

response, NIH reconvened NSABB to reconsider their original recommendation. In March, NSABB agreed unanimously to approve the full publication of a revised version of Kawaoka's manuscript and voted 12-6 in favor of publishing Fouchier's revised manuscript.[38]

The controversy over the H5N1 experiments triggered a flurry of new policies on dual-use research in the United States. In March 2012--five years after a similar proposal was first put forward by the NSABB--the United States issued a national policy on dual-use research of concern (DURC). 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." The scope of DURC subject to oversight, however, was narrowed to seven types of experiments (based on those first put forward by the Fink Committee) conducted on one of the 15 Tier 1 select agents or toxins. This new policy only applied to unclassified research conducted or funded by the U.S. government and the burden of implementation was placed on Federal agencies that conduct or fund such research. The scope of DURC oversight was broadened in 2014 to include research at any public or private research institution that receives Federal funding for life science research, even if the DURC is not being conducted with government funding. This policy also applies to foreign research institutions that receive U.S. funding for DURC research. The 2014 policy established a framework for oversight of DURC that required institutions that receive Federal funding for life sciences research to establish an Institutional Review Entity (IRE) to implement the DURC policy.

In January 2013, the influenza research community declared an end to their self-imposed pause on research.[39] Subsequently, HHS unveiled new rules governing its process for funding of GOF research with highly pathogenic avian influenza viruses such as H5N1 and H7N9.[40] In February 2013, the RAC recommended additional safety enhancements for research on mammalian transmissible HPAI H5N1 virus to supplement the biosafety requirements for HPAI H5N1 that were already delineated in the NIH guidelines.

Controversy over GOF research was renewed in 2014 in the wake of a trio of biosafety failures involving smallpox, anthrax, and avian flu that came to light in July. Although none of these incidents caused any human illnesses, the close timing of these mishaps and the fact that they occurred at elite biomedical research institutions such as NIH and CDC heightened concerns about the safe conduct of research with pathogens with enhanced virulence or transmissibility. In response to these incidents, in October 2014 the White House issued a moratorium on funding new GOF studies on influenza, SARS, and MERS, asked scientists engaged in such research to halt their experiments, and announced that it would initiate a "deliberative process" to develop a new policy on dual-use GOF research. The NSABB led this 18 month-long deliberative process which consisted of five meetings of the board, the commissioning of a technical report analyzing the risks

[38] Maher B. "The Biosecurity Oversight," *Nature* 2012; 485: pp. 431-434.
[39] Fouchier R.A.M., García-Sastre A., and Kawaoka Y. "Transmission Studies Resume for Avian Flu," *Science* 2013; 339(6119): pp. 520-521.
[40] HHS, A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets 2013;; and Jaffe H., Patterson A.P., and Lurie N., "Extra Oversight for H7N9 Experiments," Science 2013; 341(6147): pp. 713-714.

and benefits of GOF research and an ethical study of this research, and two workshops held by the National Academies of Science to solicit the input of stakeholders. This deliberative process culminated in a set of recommendations in May 2016 from the NSABB for oversight of gain-of-function experiments.[41]

These recommendations formed the basis for guidance issued by the Office of Science and Technology Policy (OSTP) in the White House in January 2017. OSTP's Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) dubbed the P3CO Framework, recommended that Federal agencies adopt new mechanisms to govern the creation, transfer, and use of potential pandemic pathogens with enhanced virulence and/or transmissibility. Once an agency has adopted such a policy, it will be able to resume funding research that was suspended by the October 2014 moratorium on gain of function studies with influenza, MERS, and SARS.[42]

In December 2017, HHS issued its policy on the oversight of research involving enhanced potential pandemic pathogens. This new policy is broadly similar, but not identical to, the corresponding guidance from the OSTP, which itself drew heavily from the NSABB report. At the same time that HHS issued its policy, it also announced that it was resuming funding of research into enhanced potential pandemic pathogens. The HHS P3CO framework is notable for a few reasons. First, the framework's approach to DURC is not based on lists of experiments or on specific pathogens, but instead takes a risk-based approach that focuses on the attributes of modified organisms. While the identity of starting organisms is central to previous DURC policy, the P3CO framework emphasizes the importance of organisms' properties once the experiment is over. Second, the policy is more prescriptive about how the review will be undertaken. The HHS P3CO framework mandates that review of proposed projects that may involve the creation or use of enhanced potential pandemic pathogens will be conducted by a department-level, multidisciplinary review group including experts with experience in scientific research, biosafety, biosecurity, medical countermeasures, law, ethics, public health preparedness and response, biodefense, select agent regulations, and public health policy. Third, review process includes 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 frameworks makes this trade-off explicit. Fourth, the final criterion in the Health and Human Services review process is to determine whether or not research is "ethically justifiable." The department-level review committee, is encouraged to consider to what extent the experiment represents non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship. Previous guidance for dual-use research of concern was focused strictly on scientific criteria for assessing the risks and benefits of dual-use research. In other ways, the framework does not represent a departure from previous policy such as its exemption of privately funded research and limited transparency.[43]

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[41] National Science Advisory Board for Biosecurity (NSABB). *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*; 2016: https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

[42] Office of Science Technology and Policy (OSTP), Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO) 2017.

[43] Koblentz G.D. and Klotz L.C. "New pathogen research rules: Gain of function, loss of clarity," *Bulletin of the Atomic Scientists* 2018; https://thebulletin.org/new-pathogen-research-rules-gain-function-loss-clarity11540

Evaluation of Biosafety and Biosecurity Oversight Regimes

The biosafety and biosecurity regimes in the United States developed sequentially and largely in parallel. As a result, these regimes are increasingly fragmented and stovepiped: biosafety, biosecurity and dual-use research all handled by different organization at the Federal level and possibly at the institutional level. The relevant policies governing the safe, secure, and responsible conduct of life sciences research are found in multiple locations which span the continuum from codes of conduct and standards to guidelines to regulations to legislation. It is worth stepping back to compare and contrast these regimes along several dimensions to inform our thinking on how to adapt them to the new challenges posed by genome editing: anticipation, adaptiveness, institutionalization, and comprehensiveness.

Degree of Anticipation

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 changes.[44] This reactive model of policy-making, however, is widely viewed as being unsuited for an era of rapid technological change. The combination of frustration with this incremental and failure-driven policy-making process and the potential risks and inherent uncertainties associated with some aspects of life sciences research is the wellspring for those who favor the precautionary principle which seeks to slow down science until policy can catch up. The way in which scientists and policy-makers have tried to anticipate and mitigate risks holds valuable lessons for how to approach the governance of genome editing.

This model of policy development is most readily apparent in the biosecurity domain. The major U.S. biosecurity policies were enacted in direct response to specific incidents associated with biological terrorism. The case of Larry Wayne Harris led to the establishment of the original program to govern the transfer of select agents in 1996. The terrorist attacks on September 11 and the Amerithrax case in 2001 led to the expansion of the select agent program to cover possession of these agents. The 2008 revelation about the role of Bruce Ivins as the Amerithrax perpetrator led to the 2010 executive order that introduced personnel reliability programs for Tier 1 select agents. Perhaps in part because biosecurity policy is enshrined in legislation and implemented through regulations, policy in this area is the slowest to change.

Within the domain of dual-use research, a handful of scientific articles in the early 2000s increased awareness of this issue among policy-makers. It took a major controversy, however, over the creation of mammalian-transmissible H5N1 avian influenza to galvanize policy-makers to take concrete steps to address the potential risks posed by dual-use research. Between 2012 and 2014, a suite of new policies were put into place to govern not only the funding of future experiments of this type, but dual-use research with a broader range of dangerous pathogens. Likewise, the October 2014 funding pause on GOF research was the direct result of a spate of biosafety mishaps at premier US biomedical research institutions over the summer.

[44] On the role of focusing events in revolutionary policy changes, see Birkland T.A. *After disaster: Agenda setting, public policy, and focusing events*. Washington, DC: Georgetown University Press; 1997; and Birkland T.A. *Lessons of Disaster: Policy Change after Catastrophic Events*. Washington, DC: Georgetown University Press; 2007. On the theory of punctuated equilibrium in evolutionary biology, see Gould S.J. *Punctuated Equilibrium*. Cambridge, MA: Harvard University Press; 2007.

The one area of dual-use research that defies this reactive model of public policy-making is synthetic biology. In 2009, two major groups of DNA synthesis companies adopted codes of conduct related to biosecurity. This initiative was supplemented by a HHS-led effort to develop voluntary customer and sequence screening guidelines for use by U.S.-based DNA synthesis firms. While there had been numerous press articles and studies that highlighted the potential risks of synthetic biology, there had been no specific safety or security incident that galvanized these initiatives. It is worth noting, however, that these guidelines are strictly voluntary; unlike the biosecurity regulations that have been in place since 1996 and the dual-use research policies that have been in place since 2012. The synthetic biology community has been more proactive addressing potential risks, but the community generally adheres to the self-governance model pioneered by the molecular biology community in the 1970s.

Biologists have been the most proactive addressing potential risks in the field of biosafety. The Asilomar conference that led to the establishment of the RAC at NIH and the rDNA Guidelines has become synonymous with an enlightened approach to risk management that rests on the ability of scientists to recognize the risks posed by their research and a willingness to take practical steps to minimize those risks while not imperiling the beneficial aspects of their research. While NIH was given authority by the molecular biology community to devise the rDNA Guidelines, the RAC has been dominated by scientists from that community, ensuring a degree of control over the policy formulation and implementation process. That the NIH Guidelines were the result of an organic, decentralized, bottom-up process is in stark contrast to biosecurity regulations which tend to be the result of a centralized, top-down process. This may also be a function of the perceived urgency to fix gaps in biosecurity revealed by incidents such as the Larry Wayne Harris case and the anthrax letters which precludes the lengthy consensus-building process inherent in bottom-up approaches.

It is worth noting that in the two areas, biosafety and synthetic biology, where biologists took the lead in acknowledging and addressing the risks posed by their research before a highly publicized incident prompted policy-makers to intervene are the two areas where they were most effective at designing and implementing self-governing oversight mechanisms. The reactive model also predicts that biosafety and biosecurity will remain stovepiped. While policy in each domain has spilled over in some ways to the other domain, they each rely on different legal and bureaucratic sources of authority. As each policy domain evolves independently, the result is an increasingly disjointed agglomeration of policies with overlapping edges. At the conclusion of the White House-mandated "deliberative process," NSABB recommended that "oversight mechanisms for GOF research of concern should be incorporated into existing policy frameworks when possible."[45] Neither the OSTP nor the HHS P3CO frameworks achieve that objective. Given a dramatic incident that calls into question the policy frameworks governing safety, security, and responsibility, this is unlikely to change in the near future.

Degree of Adaptiveness

The degree to which policy in these domains can adapt to changing circumstances also varies. The most adaptive so far are the NIH rDNA guidelines promulgated by the RAC. The NIH Guidelines

[45] National Science Advisory Board for Biosecurity (NSABB). *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*; 2016: https://osp.od.nih.gov/wp-content/uploads/2016/06/NSABB_Final_Report_Recommendations_Evaluation_Oversight_Proposed_Gain_of_Function_Research.pdf

underwent a major revision in 1978 and were then modified roughly every three months for several years.[46] The RAC had three important features. First, it was housed in NIH which is not a regulatory body and therefore adherence to its guidelines were strictly voluntary (although compliance was a condition of funding from NIH). Second, this type of oversight provided much more flexibility for amending the guidelines compared to traditional regulations. Indeed, the guidelines were amended regularly to account for scientific developments, most of which demonstrated that the safety hazards posed by rDNA research was less than initially expected and therefore certain types of restrictions could be eased or lifted.[47] Third, the RAC was initially composed entirely of scientists and has remained dominated by scientists on the premise that they have the expertise needed to assess the benefits and risks of research and devise precautions that can reduce risks while not unduly impeding scientific progress.

The other pillar of biosafety, the BMBL, is less adaptive than the rDNA Guidelines on the macro level, but equally adaptive at the micro level. Although CDC and NIH have the authority to revise the BMBL, given the breadth and depth of its coverage, the revision process is a collective, collaborative one that engages a variety of non-government stakeholders.[48] As a result, the BMBL is currently on its 5th edition after more than 20 years. The strength of the BMBL is that it provides biosafety professionals with the knowledge and tools to assess the risks posed by existing and novel infectious agents and institute commensurate biosafety practices.

The Select Agent regulations are the least adaptive set of policies since they originate in statute and are implemented via Federal regulations (US Code). CDC and APHIS are required, however, to review and republish the lists of Select Agents and toxins on at least a biennial basis. To address emergent biosecurity issues, it has been necessary to charter special interagency working groups to propose revisions to the Select Agent regulations. In 2010, the Federal Experts Security Advisory Panel was chartered to update the Federal Select Agent Program in light of the Ivins revelations, and they were rechartered in 2014 in response to concerns with the safety of GOF experiments with potential pandemic pathogens. The 2014 safety mishaps also led to the creation of a Fast Track Action Committee within the National Science and Technology Council in the White House to recommend enhanced biosafety and biosecurity measures. Over time, the Select Agent regulations have become increasingly prescriptive, especially with regard to Tier 1 agents and toxins.

Since DURC policy was first promulgated in 2012, adaptation has so far been only marginal. The scope of the policy was expanded in 2014 from Federally funded or conducted research to research conducted at Federally funded institutions which was a major change. This overarching policy was also supplemented by a new policy issued by HHS to exercise tighter oversight of decisions to fund GOF research--but it was narrowly tailored to address only H5N1 and then H7N9 avian influenza. In December 2017, HHS expanded its funding oversight to include any research with the potential to enhance the lethality and/or transmissibility of a potential pandemic pathogen. This

[46] Talbot B. "Development of the National Institutes of Health Guidelines for Recombinant DNA Research," *Public Health Reports* 1963; 96(4): p. 361.
[47] The rDNA Guidelines have been amended 26 times since 1994. https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html
[48] National Academies of Sciences, Engineering, and Medicine. Soliciting Stakeholder Input for a Revision of Biosafety in Microbiological and Biomedical Laboratories (BMBL): Proceedings of a Workshop. Washington, DC: National Academies Press; 2016.

was a major improvement over the original focus on influenza, MERS, and SARS in the original round of deliberations on gain of function research.

One advantage of the existing DURC policy is that it is agnostic about the type of technology or specific technique used to conduct the experiments of concern. The existing policy, however, was unable to accommodate the challenges posed by the broader issue of GOF regarding the creation of potential pandemic pathogens. The current DURC policy only covers specific experiments conducted on a set list of pathogens (which mirrors the Tier 1 select agents). The OSTP approach to oversight is not based on lists of experiments or pathogens, but takes a risk-based approach that focuses on the attributes of the modified organism. The resulting OSTP guidance and HHS policy reflect a basic incompatibility between the DURC and P3CO approaches to oversight which is indicative of a system that is not well equipped to adapt to change. DURC policy has therefore exhibited less adaptability than either biosecurity or biosafety. Although DURC is a relatively new policy domain and therefore has had the least opportunity to adapt to changing scientific, political, or security conditions, the scale and speed of the advances in the life sciences with which DURC must cope are far greater than what is experienced in the fields of biosafety or biosecurity.

Degree of Institutionalization

The biosafety and biosecurity regimes also differ significantly in the degree to which oversight is institutionalized, meaning the degree to which there are organizations equipped with the authority, information, and expertise to review the performance and activities of the entities being supervised and the power to enforce compliance. The Government Accountability Office (GAO) has identified five key elements of effective oversight in areas where low-probability events can have high negative consequences:[49]

- Independence: The organization conducting oversight should be structurally distinct and separate from the entities it oversees.
- Ability to perform reviews: The organization should have the access and working knowledge necessary to review compliance with requirements.
- Technical expertise: The organization should have sufficient staff with the expertise to perform sound safety and security assessments.
- Transparency: The organization should provide access to key information, as applicable, to those most affected by operations.
- Enforcement authority: The organization should have clear and sufficient authority to require that entities achieve compliance with requirements

The area with the highest degree of institutionalization is the safety and security of labs working with Select Agents. The CDC and APHIS are Federal agencies staffed by experts that are empowered by legislation and regulations to conduct inspections and levy civil and criminal penalties on institutions found to be in violation of safety and security regulations. This oversight, however, is not without its problems.[50]

[49] GAO, High Containment Laboratories: Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens, GAO-18-145. Washington, DC: GAO; 2017.
[50] Harris E.D. "Dual-Use Threats: The Case of Biotechnology," in Elisa D. Harris, ed., *Governance of Dual-Use Technologies: Theory and Practice*. Cambridge, MA: American Academy of Arts and Sciences; 2016: p. 83; and Morse S.A. "Pathogen Security-Help or Hindrance?" *Front Bioeng Biotechnol.* 2014; 2: p. 83. doi:10.3389/fbioe.2014.00083

The safety of research with rDNA and synthetic nucleic acids relies on a long-standing system of oversight that uses a tiered approach with primary responsibility for review being conducted at the local level by IBCs, and the RAC conducting review upon request and for "restricted experiments." One weakness in this system is a lack of independence at the local and Federal levels since the IBC is reviewing research conducted by PIs at its own institution and the RAC is part of NIH which is the typically the agency that funds the research being reviewed. Another weakness is that the NIH 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.[51] Another longitudinal study found improved compliance rates among IBCs due to greater outreach by NIH and adverse media attention.[52] 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. At the same time, this study concluded that "there may be many IBCs that lack adequate staffing and oversight, and that do not provide the required training."[53] Finally, although NIH has the power to terminate funding for violation of the Guidelines, it has never done so. A final weakness of biosafety oversight is that it is completely voluntary for institutions, such as pharmaceutical and biotech companies, that do not receive NIH funding. 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.

Dual-use research relies on a tiered oversight system similar to that used for the safety of rDNA research. The IRE, which may be the same as, a subset of, or completely separate from the IBC, is responsible for reviewing research for dual-use research of concern. DURC is the area that the fewest number of IBCs reported have conducted training on.[54]

[51] Sunshine Project, *Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research*. Austin, TX: Sunshine Project; October 2004; and Race M.S. and Hammond E. "An Evaluation of the Role and Effectiveness of Institutional Biosafety Committees in Providing Oversight and Security at Biocontainment Laboratories," *Biosecurity and Bioterrorism* 2008; 6(1): pp. 19-35.
[52] Hackney R.A. Jr., Myatt T.A., Gilbert K.M., Caruso R.R., and Simon S.L. "Current Trends in Institutional Biosafety Committee Practices," *Applied Biosafety* 2012; 17(1): pp. 11-18.
[53] Ibid.
[54] Ibid.