Roadmap for Biosecurity and Biodefense Policy in the United States

Roadmap

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Roadmap

In 2001, Lasker Prize winner, Matthew Meselson, called the 21st century the age of biotechnology.(13) The most recent market predictions suggest the global market for biotechnologies will reach $727.1 billion by 2025, with the largest growth in the health and agriculture sectors.(12) The rapid pace of change within the life sciences and biotechnology challenges current systems designed to leverage new capabilities and to prevent harms. These changes are driven by many factors, including, but not limited to, the influx of non-traditional practitioners, investment by a diversity of funders, social acceptance of health applications, increased agricultural needs, and the increasing convergence of physical, computational, and life sciences. Together, these factors lead to transformative changes in biotechnology that enable new knowledge gain and new applications. Examples of biotechnologies that have altered current life science capabilities include precision medicine, systems-level analysis, bio-based systems for chemical production, synthetic biology, tissue printing, additive biomanufacturing, neural networks, and artificial intelligence. Government and non-government funders have recognized the potential for these advances to improve health, agriculture, environmental monitoring and remediation, and energy. Within the U.S. government, the Department of Defense has been a leader in promoting and investing in these and other similarly transformative technologies to improve warfighter health and capabilities. Their efforts are enhanced by the National Institutes of Health, National Science Foundation, and Department of Energy Office of Science investments in basic research in these fields. In addition, these funders benefit from a few creative scientists and technologists who are willing and able to undertake high-risk, high-reward research, several of which involve integrating different disciplinary approaches, technologies, and information to achieve something new.

At the same time, research and development in these and other areas of biology and biotechnology are being supported to address current societal needs in health and defense. For example, the Fiscal Year 2018 Omnibus Appropriations Bill includes: a) $37.1 billion for the National Institutes of Health (NIH) to support basic research on Alzheimer's disease, opioid addiction, map of the human brain (through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative), precision medicine, combatting of antibiotic resistant bacteria, and a universal flu vaccine;(14) b) $5.26 billion for the National Institute of Allergy and Infectious Disease (NIAID), the primary institute within the NIH that funds biodefense research; c) $22 billion for the Department of Defense to support a variety of research and facility maintenance activities, including funding basic and applied research, development, testing, and evaluation; and d) $509.8 million for the Department of Homeland Security Science and Technology Directorate to support research and development.(15)

Specifically focusing on biodefense (i.e., capabilities for countering biological threats), fundamental research (i.e., basic and applied research whose results are intended to be shared with the scientific community) includes identification and characterization of pathogens considered as priority threats to the United States, development of modeling, knowledge, and technologies for pathogen detection and monitoring (i.e.,

biosurveillance), pre-clinical research and development of medicines against high-priority pathogens (i.e., medical countermeasures), and development of new methodologies for attribution (e.g., microbial forensics). Based only on funding levels of basic and applied research and development, the primary U.S. government entities that support biodefense or health security activities are NIAID, Centers for Disease Control and Prevention (CDC), Food and Drug Administration, Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense, specifically the Defense Threat Reduction Agency, U.S. Army Medical Research Institute of Infectious Diseases, and Defense Advanced Research Projects Agency. On occasion, other U.S. government agencies (e.g., Department of Homeland Security Science and Technology Directorate and U.S. Department of Agriculture Animal and Plant Health Inspection Service) have supported basic and applied research for biodefense. Most of the biodefense funds have been appropriated for broader preparedness and response efforts, agriculture and food defense, advanced product development, and risk, threat, and vulnerability assessment.[1]

Implications of the Evolving Biotechnology Landscape

The potential for benefit and harm exists within the global context of biotechnology research, development, and application, where individuals, institutions, and countries have significant influence over whether and to what degree science advances, how science and technology are applied, and who owns information and technologies. Four primary changes have occurred during the past 10-15 years that have, and will continue to, alter the biotechnology landscape: 1) expansion of the funding landscape to include venture capital firms and public crowdsourcing in addition to private industry, philanthropic organizations, and government funders; 2) increasing convergence between life-science and non-life-science disciplines; 3) broadening of practitioners of biology to include citizen scientists and non-life scientists; and 4) globalization of biotechnology capabilities. Box 1 describes each of these changes in detail. In addition, increased access to scientific publications through open access journals and policies, and experimental videos through online journals and YouTube (and other similar platforms) are enabling greater access to biological research and helping to lower the barriers of entry to working with biology. Furthermore, as calls for improving reproducibility in science increase and acted upon, the reliability and replicability of published experimental research also will increase. Together, these changes and trends define the current landscape in the biological sciences and biotechnology.

[1] Before 2001, biodefense research was conducted by a small group of scientists, in large part because annual funding levels were extremely low. The Department of Defense, which was responsible for medical defense research, was appropriated $60 million annually in fiscal years 1999, 2000, and 2001. At the same time, the NIAID supported basic research on overlapping pathogens at a funding level of $270 million in fiscal year 2001. Shortly after the 9/11 attacks, DoD received an annual increase of $30 million in biodefense funding whereas HHS received a budget increase of more than $1.5 billion. Funding for biodefense continued to increase over the past 17 years, fluctuating annually because of scope and political interest.

Box 1. Changes in the Biotechnology Landscape

The **funding landscape** for research conducted in the United States has expanded well beyond U.S. government funders and disease-specific philanthropic organizations to include Silicon Valley venture capitalists, and foreign governments, and the general public through crowdsourcing platforms such as Kickstarter and Experiment.com. Along with funding professional scientists, these sponsors have provided financial support for teams of undergraduate or high school students participating in the International Genetically Engineered Machine Competition. In addition to these new sponsors of biological science and technology, private industry, academic institutions, and other research institutions have begun supporting research that the U.S. government is not willing to support (e.g., modification of live human embryos(1)) and outside the traditional disciplinary boundaries (e.g., synthetic biology and big data analytics). The change in the funding landscape simultaneously enables innovation and entrepreneurship within the amateur and professional science and technology communities, while also demonstrating the limitations of federal requirements that are tied to U.S. government funding. (See Appendix 1 on the synthesis of horsepox virus.)

The **convergence of life-science and non-life-science disciplines** are leading to new scientific discoveries, capabilities, and applications. In some ways, this convergence involves the support for and conduct of cross-disciplinary science such as data science and the life sciences, which has enabled the fields of systems biology and precision medicine, or material science and the life sciences, which has led to additive biomanufacturing (i.e., 3D and 4D printing of tissues). In other ways, convergence involves the use of engineering principles to "design" and "build" biological systems. This description of convergence is most closely associated with synthetic biology, which at its foundation is the application of engineering concepts (specially, the design-build-test cycle) to biology; the actual methods and materials involved in synthetic biology are common to genetic engineering, which first emerged in the late 1960s. A third way convergence has been used is the repurposing of biological organisms and molecules from their natural functions to a man-made function. For example, DoD has invested in research to create bio-based sensors that can detect radioactive and non-radioactive molecules,(5) and Microsoft Corp has supported research to use DNA molecules to store data, including image, video, and audio information.(6) New educational and research programs have been established to promote and drive innovation in multidisciplinary science.

The demographic of **practitioners** who work with biological organisms and molecules has expanded well beyond the interdisciplinary life scientists and clinicians to include researchers with expertise in engineering, computer, data, materials, physical and chemical sciences; artists; citizen scientists; and community laboratory members. The influx of practitioners into biology has pushed the boundaries of scientific achievement and risk, enabling innovation and entrepreneurship in biology and biotechnology while also creating new vulnerabilities that may result from careless, uninformed, or malicious individuals. A timely and illustrative example of this is the field of synthetic biology, which emerged when a group of computer scientists and engineers at MIT asked whether functional biological systems could be created using standardized biological parts. This initial question, which was asked of undergraduate engineering students taking a summer course at MIT, led to the creation of the International Genetically Engineered Machine (iGEM) competition, which has encouraged unconventional thinking about biology, development and sharing of genetic engineering materials and methods, and entrepreneurial spirit.(7) In fact, on its website, iGEM highlights synthetic biology companies that started out as teams in the competition. At the same time, the statements about creating new or unnatural biological organisms in a deliberate and predictable manner has elicited significant concern among the biosecurity community in the United States and internationally. In addition to the synthetic biology community, entrepreneurial members of the amateur biology community (so-called Do-it-yourself Biology (DIY Bio) community) have created companies to provide laboratory equipment and materials that fellow citizen scientists cannot obtain from the established biotechnology companies. Still other amateur scientists have created companies that conduct extremely risky, and ill-advised activities (e.g., amateur biologists injecting themselves with DIY genome editing tools or viruses(8-10)).

Global investment in the biological sciences and biotechnology has increased because of two primary drivers: 1) national-level interest in addressing human health needs (specifically, reducing chronic and infectious disease incidence and burden), improving agriculture and food availability and quality, and promoting economic growth;(11) and 2) international interest in building capabilities to promote development and to prevent, detect, and treat communicable and non-communicable disease. The global biotechnology market in 2016 was $369.62 billion with the largest market share in North America followed by Europe and the Asia Pacific region.(12) China and Brazil are among the countries actively growing their biotechnology investments.

The dramatic changes in the biotechnology landscape presents new opportunities for building U.S. capabilities to counter biological, chemical, and radiological threats and new challenges to established assessments and concerns about biological threats. This dichotomy has led some national security experts in the U.S. government to question the need for certain types of science fearing the risk may be greater than the reward, whereas others focus more on the benefits and promise of new advances and applications in biotechnology for addressing critical capability gaps in civilian and military preparedness and response efforts. Still others, continually raise concerns about "technology surprise" and the inability to stay ahead of changes in science and technology, including biotechnology, that could cause an unmatched advantage to a U.S. adversary. Congress has passed laws attempting to address some of these concerns. For example, the May 2017 Consolidated Appropriations Act includes a section requiring the intelligence community to assess new advances and applications of biology and biotechnology as they relate to U.S. "competitiveness in the global bioeconomy", including an evaluation of "the risks and threats evolving with advances in genetic editing technologies" and their implications on biodefense needs.(16) Just five months earlier, Congress passed the National Defense Authorization Act of 2016, which included a section requiring the Departments of Defense, Health and Human Services, Homeland Security, and Agriculture to develop a new biodefense strategy for the United States.(17) The law specified a review of existing policy and programs, articulation of biological threats, evaluation of agency roles and responsibilities, and development of recommendations to improve biodefense capabilities. This law encompasses the two main way in which the United States seeks to counter biological threats: 1) biosecurity, which specifically focuses on preventing theft, diversion, or deliberate malicious use of biological sciences knowledge, skills, materials, and technologies to cause harm; and 2) biodefense, which involves the development of capabilities and knowledge-based to assess, detect and monitor, treat (or vaccinate against), and respond to biological threats.

In addition to the congressionally-mandated activities, the Environmental Protection Agency, U.S. Department of Agriculture, and Food and Drug Administration updated the Coordinated Framework for Regulation of Biotechnology in 2017.(18) The purpose of the update was to increase confidence in the system for regulating biotechnology products and to prevent "unnecessary barriers to future innovation and competitiveness" in the biotechnology sector. Although this Framework focuses on safety and environmental protection regulations, it overlaps with investments in biological products to enhance U.S. capabilities to detect, prepare for, and respond to chemical, biological, radiological, and nuclear threats. For example, the Department of Defense has invested in synthetic biology research to develop bio-based sensors of biological and nuclear materials, improved medical countermeasures against biothreat agents, and organisms that can be used for bioremediation. Beyond genetic modification technologies, DoD has supported the application of big data analytics to establish and improve early warning of biological threats (i.e., biosurveillance),(19-22) genomics to improve medical care for the warfighter and veteran,(23-26) and neuroscience and mechanical engineering to create neuroprosthetics for military personnel who have lost limbs in combat.(27)

The broader implications of the changing biotechnology landscape are not well-understood, in part because advances are occurring at an alarming pace and increasingly off-shore. Harnessing new capabilities afforded by biotechnology may become challenging if new applications are being explored in unfriendly countries. Similarly, detecting and mitigating vulnerabilities or risks associated with new biological sciences advances and applications often is difficult, particularly if the international community is unaware of these advances or applications until after they are published. The shifting landscape exacerbates these and creates new challenges to any policy or programmatic efforts for maximally leveraging science and technology (S&T) advances and reducing national security risks. These challenges include: 1) variability in funder priorities and ethical, safety, and security norms; and 2) disproportionate economic and commercial advantage to adversarial countries investing in (or stealing) scientific information as was observed by the semiconductor industry. Within the biotechnology sectors, transfer of technology, skill, and knowledge to foreign countries (through funding and/or theft) is occurring. Lessons for countering this problem may come from non-life-science fields, such as the information technology sector, which incentivizes scientists to maintain the knowledge base, research capabilities, and skills in the U.S.

The Current State of Biosecurity and Biodefense Policy

As a part of this study, the authors conducted a systems-based analysis of the U.S. biosecurity and biodefense landscape in 2017 and 2018. The figures included in this section were created as part of this analysis, which is described in detail in the Policy Analysis chapter.

The current state of biosecurity and biodefense policy in the United States is bifurcated with one group of policies focused on preventing theft, diversion, and deliberate malicious use of biological materials, knowledge, skills, and technologies in the United States and internationally, and a second group of policies focused on building scientific and technical capabilities for early warning, preparedness, and response to natural, accidental, or deliberate biological threats. (Figure 1) This two-group system has resulted from the iterative and responsive process of biosecurity and biodefense policy-making during the past one hundred years.

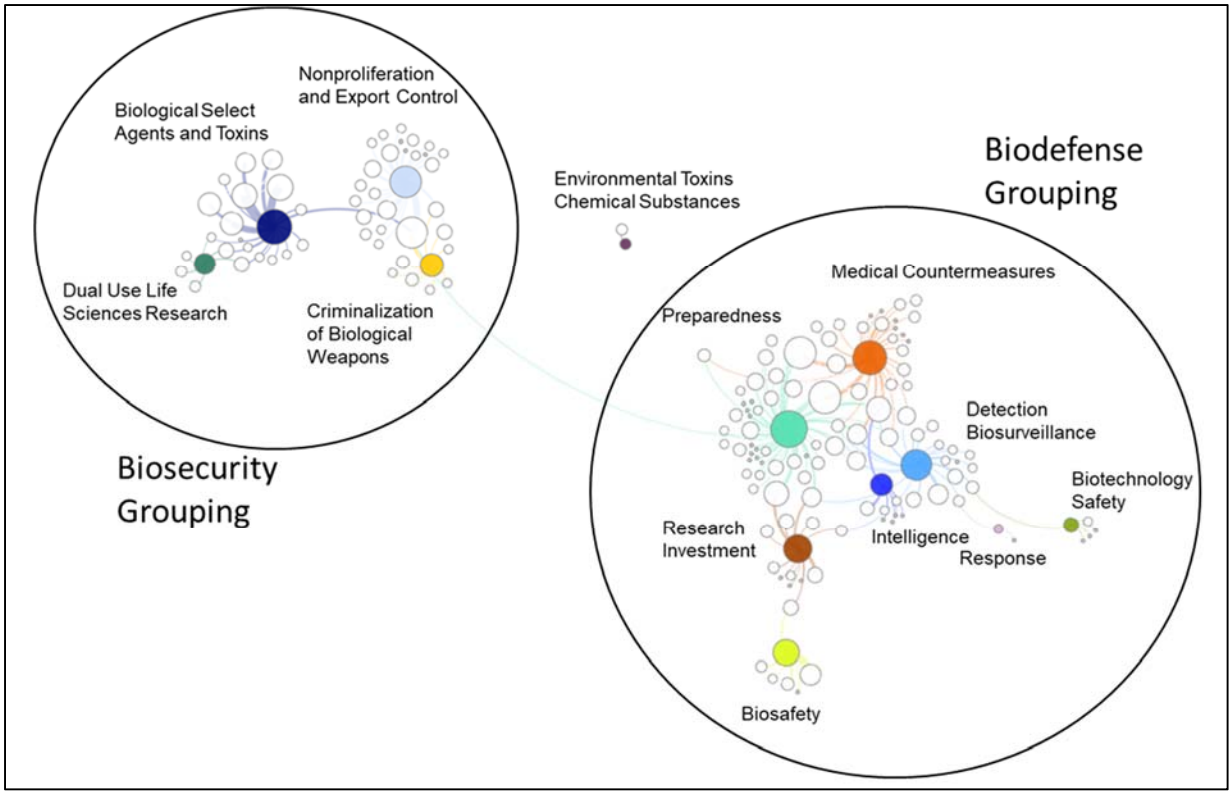

Figure 1. Relational map of U.S. biosecurity and biodefense policy by policy subject. Each white circle is a unique U.S. Code, international agreement or partnership, Executive or agency-level policy, program activity (if not already associated with a U.S. Code, international partnership, or agency-level policy), guidance, and guidelines. The size of the circles reflects the number of policies that are associated with a biosecurity or biodefense subject area. The colored circles are nodes signifying subject area. The size of the nodes reflects the number of policies associated with each subject area and the distance between nodes reflects the degree to which policies are linked based on the underlying relational database. The lines reflect direct relationships between policies and subject areas based only on existing policies. This map does not reflect associations of subject area based on conceptual similarities, but rather associations by direct links between existing policies.

As new technologies that change extant scientific capabilities are developed, as harmful incidents involving biological agents occur, or as security experts raise concern about experiments and/or information, policy-makers initiate efforts that have led to new laws and regulations, guidance, guidelines, or programs. Figure 2 illustrates the reactive nature of U.S. policy for biosecurity and biodefense. Several U.S. government agencies, local public health stakeholders, and members of the broader scientific community are responsible for implementing these policies.

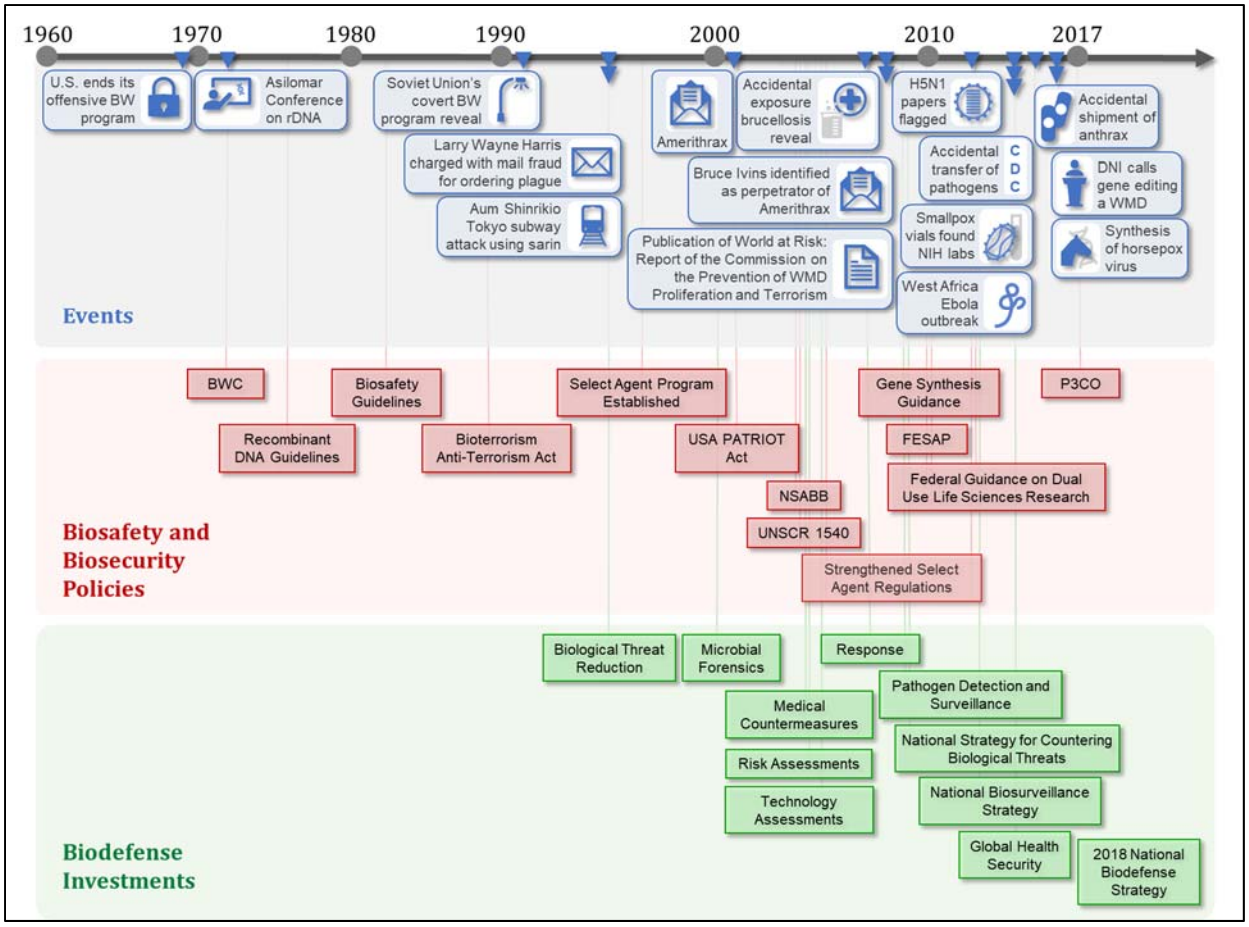

Figure 2. Schematic illustrating the reactive nature of U.S. biosecurity and biosafety policies and biodefense investments during the last fifty years.

Oversight of biological science activities, whether research or diagnostic, are governed in three ways. The first is legal authorities, which are provided by statutes and may be implemented through regulations. These laws pertain to any activities or entities that are specified in statutes and regulations, and often are not tied to funding source. Examples of these include the Biological Weapons Anti-terrorism Act of 1989, Project Bioshield Act of 2004, export control regulations, Biological Select Agents and Toxins Regulations, and occupational health and safety regulations. The second way biological activities are governed is through guidelines and guidance that are required of entities that receive funding from the federal government. These policies include the U.S. government policies on dual use research of concern, NIH Guidelines for Recombinant and Synthetic Nucleic Acids, and the HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens. Because these policies are tied to federal funding, they have no ability to govern research activities not funded by the U.S. government. The third governance approach involves voluntary policy implementation of unregulated science or entities. For example, approximately 40% of private industry in the U.S. voluntarily have created institutional programs and policies to review and oversee research involving recombinant or synthetic nucleic acids. For pharmaceutical, biotechnology, and other private companies

which do not receive financial research support from the U.S. government, the NIH Guidelines for Recombinant and Synthetic Nucleic Acids are voluntary. Similarly, U.S. and some internationally-based DNA synthesis companies voluntarily follow the Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA, which aligns with industry-developed guidance for sequence and customer screening of DNA synthesis orders. Many of these policies are bounded by lists of biological pathogens, toxins, scientific activities, and/or equipment of greatest concern to security, environmental safety, and/or worker safety. In addition, and not included here, are the regulations governing research integrity, human subjects protection, and welfare of animals used in research, all of which contribute to the overall governance of biological research in the U.S. Figure 3 illustrates current governing landscape for addressing scientific responsibility in and ethical, safety, and security risks of biological research.

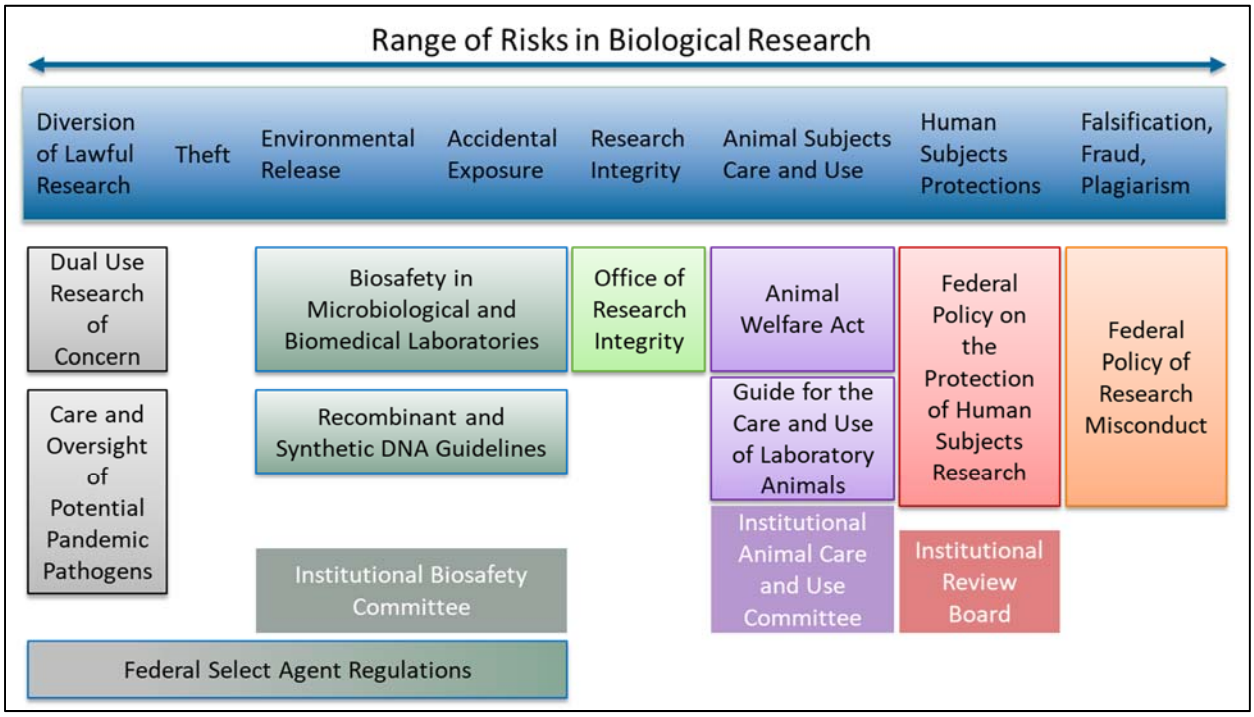

Figure 3. Schematic illustrating the current framework for governance of scientific responsibility and ethical, safety, and security risks associated with biological research.

Unlike the policy landscape for biosecurity, policies promoting investment in biodefense capability-building have sought to promote innovation within the science and technology community to generate the needed knowledge and tools. For example, several U.S. government entities, including the Centers for Disease Control and Prevention (CDC), NIH, DoD, Department of Homeland Security (DHS), and Intelligence Advanced Research and Development Activity (IARPA), have invested in biosurveillance capabilities to detect the emergence of unusual biological incidents involving biological agents, new pathogens, or laboratory-developed pathogens in animal and human populations. These efforts, which continue today, have sought to leverage advances in computer and data science to develop data analytics platforms that can integrate, sort through, and analyze vast amounts of information. In 2013, the

White House issued a National Biosurveillance Science and Technology Roadmap to help implement its 2012 National Strategy for Biosurveillance.(28, 29) Another example is DoD's interest in harnessing a variety of biological sciences, including systems biology, ecology, and behavioral sciences, to enhance military capabilities to prevent and defend against biological threats.(30) The importance of biology and biotechnology to the DoD mission was further supported by the establishment of the Biological Technologies Office of the Defense Advanced Research and Development Activity (DARPA), which seeks to harness biology and biotechnology advances to enhance national security.(31) These and many other U.S. biodefense initiatives promote development and application of cutting-edge, multi-disciplinary science to develop creative and effective solutions for countering biological threats.

Several new policy activities are anticipated in 2018. In January 2018, the Department of Health and Human Services (HHS) released its policy on care and use of enhanced potential pandemic pathogens (P3CO).(32, 33) At the present time, no other U.S. agency that funds biological research has created a corresponding P3CO policy. In March 2018, U.S. Representatives Susan Brooks and Anna Eshoo established the Congressional Biodefense Caucus to raise awareness about biosecurity and biodefense issues among members of Congress, to strengthen U.S. biosecurity and biodefense efforts, and to identify and address gaps in capabilities.(34) Also in March 2018, the 2018 Omnibus Appropriations acknowledged HHS's interest to shift oversight of the Strategic National Stockpile to HHS Assistant Secretary for Preparedness and Response (ASPR) and required the development of a U.S. strategy for global health security.(15) The Department of State (DoS) and HHS are leading efforts to define the next four years of the Global Health Security Agenda, which is an intergovernmental initiative designed to identify and address gaps in prevention, detection, and response to natural or man-made biological threats. The new National Biodefense Strategy, which was called for in the 2016 National Defense Authorization Act (NDAA), and a new National Health Security Strategy and Implementation Plan are anticipated to be released in 2018. Finally, DoD, DoS, and the U.S. Agency for International Development were involved in a Stabilization Assistance Review since May 2017, which is intended to develop a framework for foreign assistance in conflict zones and fragile states. The report of this review was delivered to Congress in April 2018 and is expected for public release later this year.(35)

Despite this high level of activity in biodefense and biosecurity policy, systematic evaluation of existing policy and implementation to identify gaps and policy solutions for addressing those gaps has not been conducted. The 2016 NDAA has called for a review of existing policies and programs, the results of which are not publicly available. In addition, the Pacific Northwest National Laboratory has identified implementing agencies of several national strategies and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.(36) To the best of our knowledge, neither of these efforts have taken a comprehensive approach to biosecurity and biodefense policy analysis. Therefore, the authors conducted a comprehensive analysis of all U.S. biodefense and biosecurity policy to identify limitations in the current policy landscape, implementation gaps, synergistic policies, and counteracting policies as a foundation for

developing the roadmap, which is described below. The full policy analysis is included in the next chapter.

Limitations of Current Policies

The policy analysis conducted as part of this study has revealed several limitations associated with the development and implementation of biosecurity and biodefense policies. These limitations fall into three main categories: a) scope and relevance of policies; b) consistency of agency-level policies promulgated to achieve government-wide objectives; c) and stakeholder contributions in policy implementation. (Table 1) Detailed descriptions of these limitations are included in the Policy Analysis chapter.

Table 1. Limitations of the Biosecurity and Biodefense Policy Landscape in the United States.

Limitations of the Scope and Relevance of Policies	Limitations to Consistency of Policy Development and Implementation Across the U.S. Government.	Limitations to Stakeholder Engagement in Policy Implementation.
Expansive policies may lack clarity about what is or is not covered under the policy, which promotes variability in policy implementation at the federal and local levels and risks affecting sectors and activities in unanticipated ways.	The current policy system is not suitable to evaluate the broader consequences of investments or regulations.	Stakeholders do not necessarily understand their roles in achieving biosecurity and biodefense objectives.
Narrow policies, especially those based on defined lists of restricted items, often prevent thorough analysis of research to anticipate and address risks early and to maximize benefits.	Federal and local stakeholders of overlapping policies may not be the same	Limited or no additional funds are available to assist key stakeholder groups comply with biosecurity regulations.
Policies that are required only at institutions that receive U.S. government funding do not necessarily cover scientific activities that are not federally funded regardless of whether they are conducted in the United States or another country, adversely affecting awareness about technological advances and of research oversight.	No consistent or common process for reviewing and overseeing research with potential for exploitation by malicious actors. Oversight of research is agency-specific.	Some tools for prioritizing biological threats result in the identification of the same agents regardless of country or situation.

Significant Gaps in Biosecurity and Biodefense Policy

During the analysis of U.S. biosecurity and biodefense policy, several capability, policy implementation, and infrastructure gaps were identified. Table 2 highlights the key gaps in each category. Detailed descriptions of these gaps are included in the Policy Analysis Section.

Table 2. Gaps in the U.S. Biosecurity and Biodefense Policy		
Capability Gaps	**Policy Implementation Gaps**	**Infrastructure Gaps**
Microbial forensics is an underinvested field in the United States and internationally.	Insufficient funds are available to support local implementers comply with biosecurity regulations, leading many to choose not to participate in research or diagnostic activities involving restricted agents.	The regional and national biocontainment laboratories are not considered critical infrastructure preventing efforts for their protection in case of an emergency.
Systems for scanning scientific advances leading to new technologies exist in offices that support or conduct research and development, but generally do not exist at the end-user or operational levels	The continuous changes to the BSAT Regulations resulted in significant challenges and delays in federal implementation and local compliance.	Very few policies and programs exist for enabling or promoting resiliency in the biodefense, health, and research sector.
Despite significant investment in biosurveillance approaches and platforms, the underlying data used to develop effective early warning methods is highly variable and uncertain.	Practical resources that enable program managers, research reviewers, and scientists assess the risks and benefits of research currently is lacking.	Very little, if any, funding has been provided for research to generate data on the effectiveness of different biosafety and biosecurity measures.
The increasing convergence of scientific disciplines, changing funding paradigm, and expansion of biotechnology practitioners suggests that greater attention is needed on evaluating the broader security implications of advances and applications that are not only focused on pathogens and toxins.	Annual and inconsistent investment in nonproliferation activities, specifically for cooperative threat reduction programs, limits long-term sustainability of partnerships and outcomes.	
	Effective measures for evaluating biosecurity policy implementation have not been developed. However, measures for evaluating a few biodefense investments do exist, each different from another.	
	No analytic framework currently exists for assessing opportunity costs of biosecurity policy development.	

The Roadmap for Implementing Biosecurity and Biodefense Policy

Drawing on the limitations and gaps identified, several *key considerations* emerge for the development of plausible roadmap that seeks to leverage the advances in science and technology while also minimizing risk. These considerations include:

- Since 2002, the U.S. government has funded significant amounts of research on high-risk, restricted pathogens to increase scientific knowledge, develop medical countermeasures (vaccines, drugs, and diagnostic tools), and develop detection methods and technologies. Many of the scientists, technologists, and engineers involved in these studies also are held responsible for compliance with U.S. biosecurity policies, including the BSAT Regulations, dual use policies, and export control requirements. This situation may result in a misalignment between scientific investment and regulation, which ultimately presents significant barriers to reaping the benefits of science and technology advances for U.S. biodefense objectives.
- The biology and biotechnology landscape has changed dramatically during the past twenty years. New funding models, practitioners, countries, and societal drivers have completely changed this landscape, but are not included as key considerations of the current biosecurity landscape. Domestic and international engagement with non-traditional funders, practitioners, international counterparts, and end-users (including the public, if appropriate) is needed to promote an environment of global support for and governance of biological science activities. This dual goal is consistent with the BWC, which prohibits only efforts and delivery systems that are intended for weapons use, and with recent calls for cross-disciplinary efforts for global health security.
- Advances in biology and biotechnology have the potential to enhance U.S. capabilities for preventing, detecting, and responding to biological threats. In some cases, these advances have been applied to specific problem-sets, such as the development of bio-based sensors using synthetic biology approaches and early warning systems using advanced biological data analytics. However, the mechanisms used to scan for promising advances, enable further innovation to address specific defense needs, and transition to operational use are limited. Improving this process would enhance opportunities for promoting creativity and communication among the biodefense and scientific communities, enabling greater harnessing of science and technology advances and applications. Furthermore, communication between the defensive and security experts could improve current capabilities for technology assessment, ultimately reducing concerns about technology surprise.
- Balancing risk and benefit objectively (i.e., without placing unsubstantiated weight on one or the other) is absolutely critical at all levels – federal, local, and international – to ensure that fears about risk or blind hope about benefits do not adversely influence any assessment of risk and benefit. Furthermore, practical resources are needed to help policy-makers, program managers, security experts, research reviewers, and scientists conduct objective assessments and learn from previous assessments. This balancing act is particularly critical given the interests in encouraging creativity and innovation within the scientific and technological communities to design, build or develop, and apply new advances to enhance biodefense, health, agriculture, and other sector-specific capabilities.

These considerations establish the premise for the following roadmap.

System-wide Roadmap

Because the biosecurity and biodefense landscape is extremely diverse and involves stakeholders from different sectors and disciplines, the roadmap articulates clear actions across all relevant stakeholder. Figure 4 presents six primary actions that the U.S. government can undertake to address current limitations and gaps of U.S. biosecurity and biodefense policy. The six actions included in this roadmap are:

- Enhance assessments of emerging biotechnologies;
- Assist the scientific enterprise for research, detection, health security, and forensics;
- Balance benefit with concern about malicious exploitation of biology and biotechnology;
- Enable innovative research and development to meet biodefense needs;
- Promote sustainability of activities;
- Characterize the biodefense research sector as a critical infrastructure to ensure assistance and guidance on recovery and resiliency.

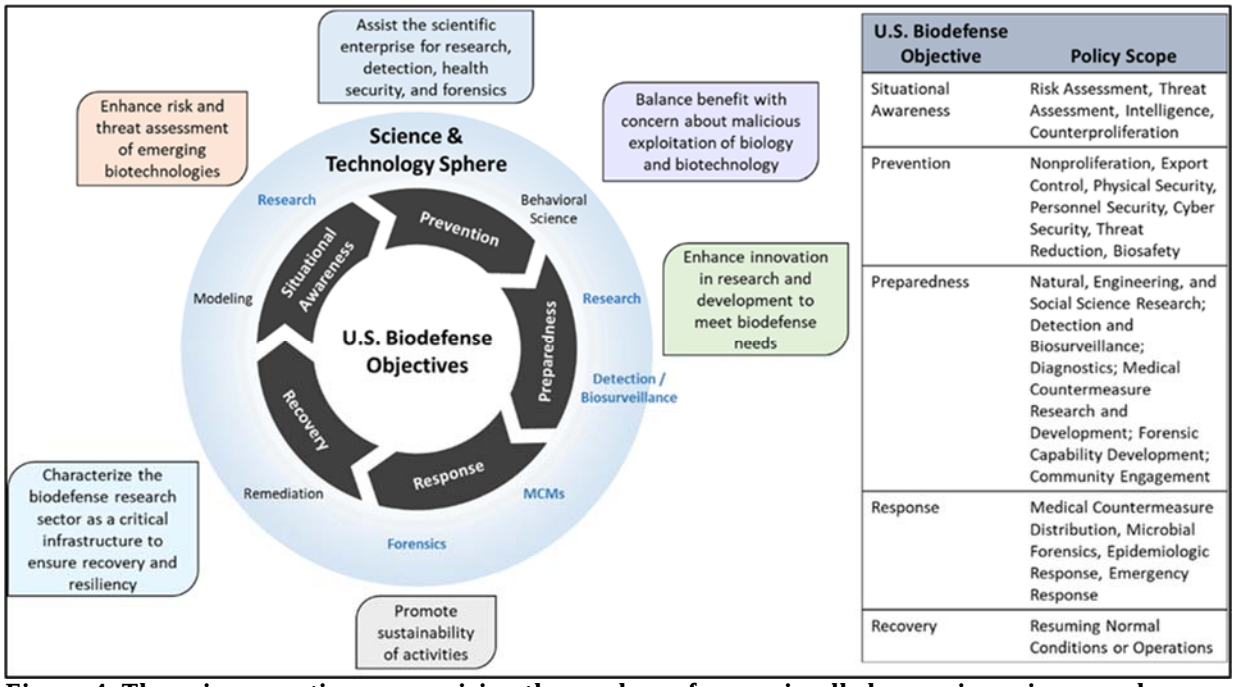

Figure 4. The primary actions comprising the roadmap for maximally leveraging science and technology advances for biodefense and minimizing biosafety and biosecurity risks. The placement of the six actions correlates with the most relevant biodefense objectives. All but one of these actions have been divided into sub-actions that contribute to their achievement. The science and technology capabilities are listed in the grey circle and placed close to the objective with which they correlate. The capabilities written in blue are discussed further in the policy analysis. The capabilities written in black are included because each is associated with one policy document. Other capabilities may exist, even though they are not included in this figure. Various U.S. government agencies have varying degrees of responsibility for each of the actions listed.

Figures 5a through 5e highlight specific steps that could be used to implement the first five actions. The primary implementor for each step is at least one U.S. government agency. Most of these actions and steps involve coordination and communication among

U.S. government stakeholders. However, a lead agency may be identified based on mission relevance, resident expertise, and available funding to support implementation and evaluation. Federal and local stakeholders, alike, may be well-suited to evaluate direct, indirect, and opportunity costs. Subsequent chapters of this report provide analytical frameworks for developing evaluation metrics of policy implementation and for examining implementation costs to various stakeholders.

The roadmap action of *enhancing risk and threat assessment of emerging biotechnology* focuses on capabilities to enhance the U.S. objectives involving situational and threat awareness. These capabilities involve providing opportunities for security experts and government personnel, more broadly, to learn about new advances in biotechnology, new applications they enable, and their technical limitations. Figure 5a includes two steps that could enhance biotechnology assessment.

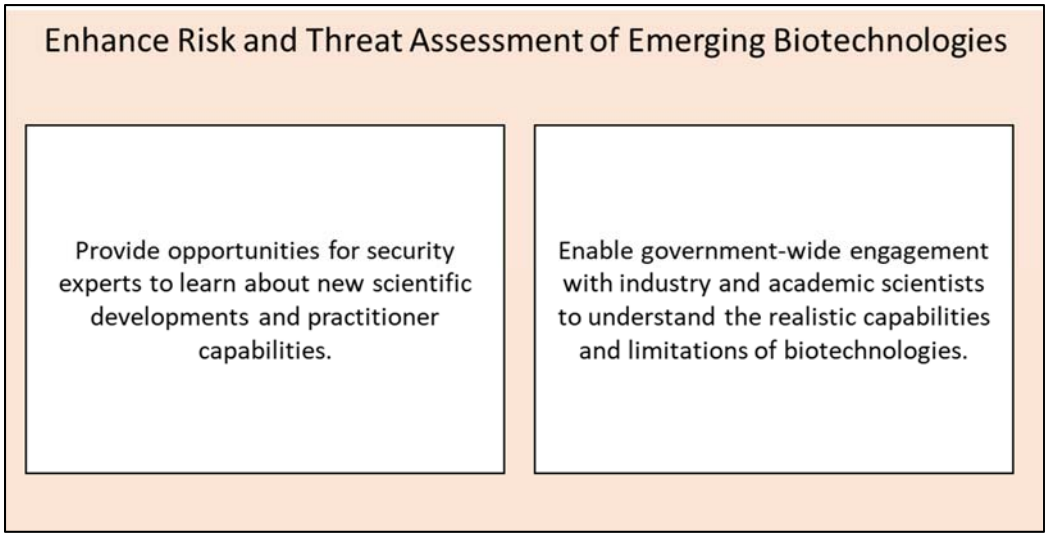

Figure 5a. Steps towards achieving enhanced emerging biotechnology assessments. The two steps listed can be conducted in parallel.

The roadmap action of *assisting the scientific enterprise involving research, detection, health security, and forensic methods* involves efforts that enable federal and local stakeholders comply with biosecurity regulations. Figure 5b includes two steps that could improve compliance with regulations through guidance and financial assistance. These steps could be done sequentially because defining changes that need to be implemented comes before needs for financial support.

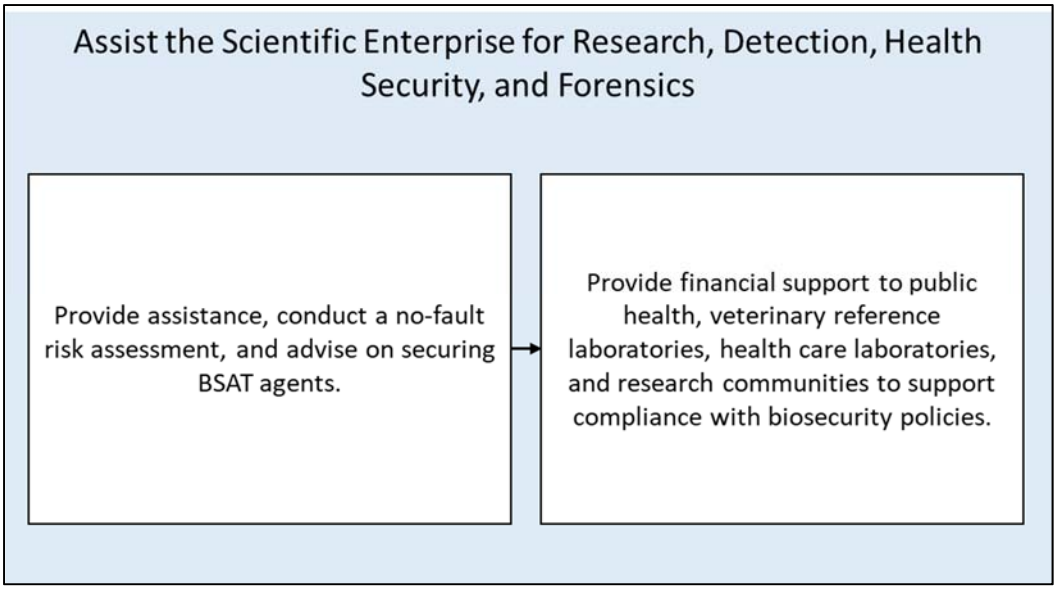

Figure 5b. Steps towards assisting the scientific enterprise that is involved in research, detection, health security, and forensics implement practices in compliance of federal biosecurity policies. The steps listed can be conducted in sequentially.

The roadmap action of *balancing benefit with concerns about malicious exploitation of biology and biotechnology* focuses on the development of resources that help federal and local stakeholders assess benefits and security risks of research objectively and share lessons learned from reviews. The steps involving stakeholder assistance for identifying and analyzing potential risks of exploitation of knowledge, skills, or technologies involves the clear articulation of outcomes of concern to ensure that guidance is not outdated as new technologies and information are created. Figure 5c presents several sequential steps towards implementation of risk and benefit assessments to maximally leverage scientific knowledge and technologies while also reducing associated security risks. These steps align most closely with prevention objectives. But, if done well, this action can result in realized benefits for preparedness and response.

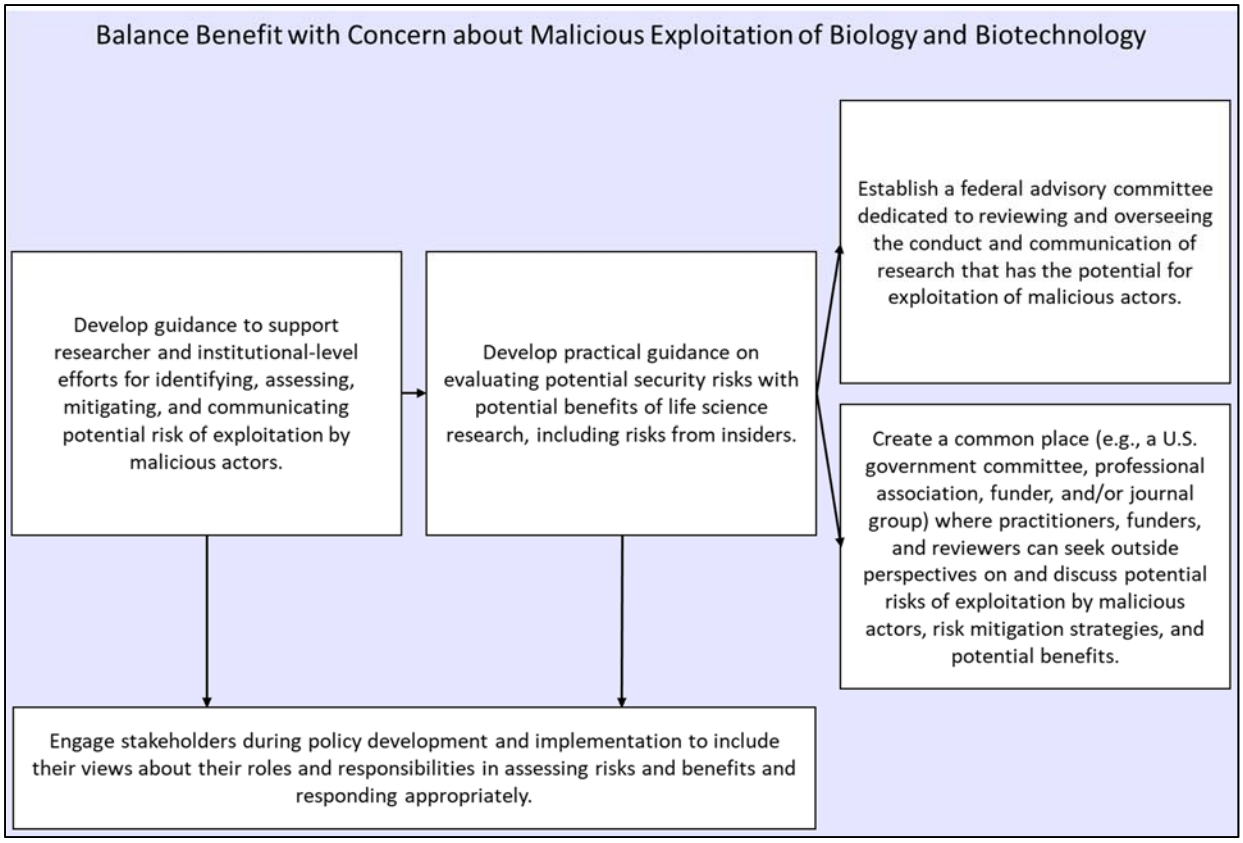

Figure 5c. Steps towards assessing and balancing the risks and benefits of biodefense and health security-relevant research. These steps could be conducted sequentially starting with the development of guidance to local stakeholders on assessing risk followed by guidance on evaluating this risk with the stated or speculated benefits. The potential benefits either are assumed from the funding initiative or project goal and rationale. These steps would be conducted in consultation with local stakeholders to ensure that the guidance reflects accurately stakeholder roles and responsibilities. A federal advisory committee that is dedicated to overseeing the conduct of research and a forum that allows opportunities for stakeholders consider different perspectives and share risk mitigation strategies could enhance objectivity in risk and benefit assessment.

The roadmap action of *enhancing innovative research and development to meet biodefense needs* focuses on enhancing the United States' ability to identify unmet or unaddressed capabilities at the national and end-user levels for which science and technology could provide solutions, support activities that enhance research capacity and workforce development, and develop approaches for encouraging more scientists and engineers to participate in the biodefense enterprise, whether as researchers, subject matter experts, and/or as policy-makers. In 2018, the Blue Ribbon Study Panel on Biodefense highlighted the need for cross-cutting budget analysis for U.S. biodefense activities,(37) a recommendation that is repeated in this roadmap. In some fields, such as vaccine and drug development, the process for basic, applied, and advanced (or translational) research is well-defined. But, in other fields, where program managers are seeking to leverage newer biological science approaches or biotechnologies to address end-user needs, the process is less well-defined, inconsistent with other processes, or not well communicated to researchers and technologists. Figure 5d includes the steps toward achieving a more informed and involved science and technology community.

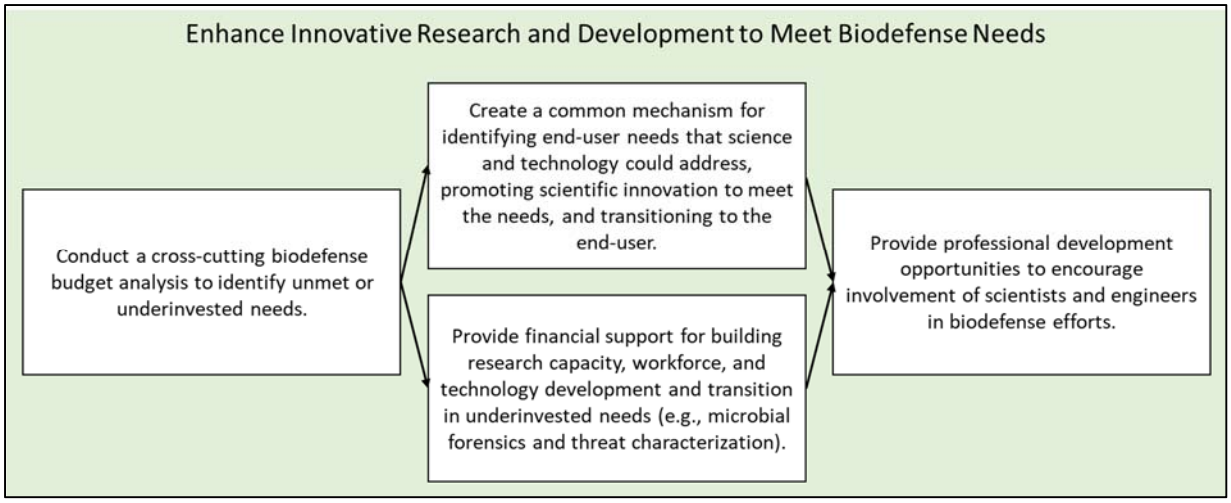

Figure 5d. Steps for enhancing research capacity to meeting unmet, underinvested, and/or end-user needs. These steps are sequential starting with cross-cutting budget analysis of biodefense and ending with opportunities to encourage involvement of scientists and engineers in the biodefense activities.

The roadmap action of *promoting sustainability* applies to all activities and stakeholders. However, the individual steps included are focused on promoting sustainability of specific activities while the U.S. government is providing financial support and well-after U.S. support ends. These steps can be conducted in parallel. The step on the left focusing on international engagement efforts with biological scientists, human and animal health practitioners, and law enforcement and emergency response personnel. The step on the right focusing on domestic efforts for maximizing benefit and minimizing risk. Figure 5e includes steps towards promoting sustainability of activities.

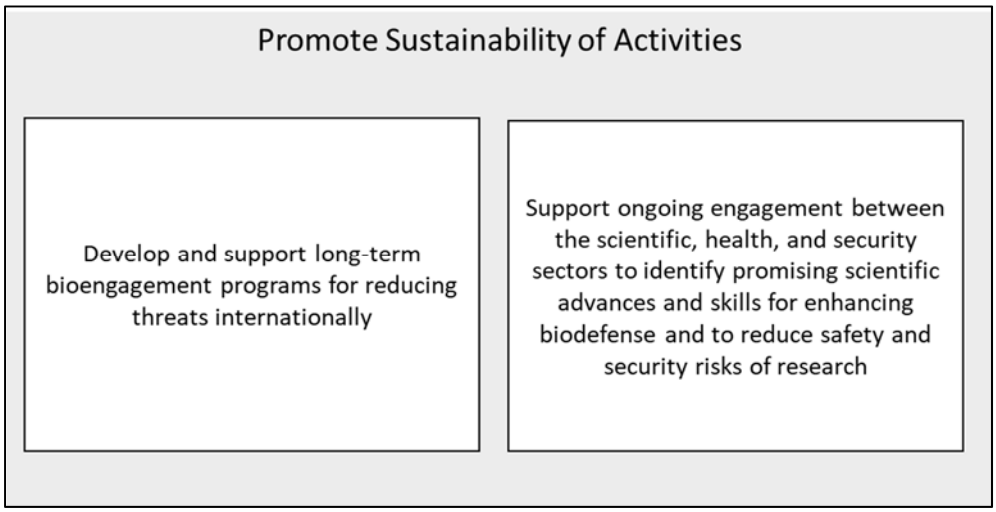

Figure 5e. Steps for promoting sustainability of activities. These steps can be conducted in parallel and apply to several stakeholders and activities.

The sixth roadmap action of *characterizing the U.S. biodefense sector as a critical infrastructure* addresses a clear gap in recovery and resiliency in this sector. Researchers regularly assist with outbreak and emergency response, lending their scientific knowledge and skills to identifying and characterizing unusual or newly

emerging biological pathogens and toxins. They conduct the foundational studies that are intended to inform medical countermeasure development, detection and monitoring of pathogens, and the development of new forensics approaches. However, the research sector is not part of the existing U.S. critical infrastructure sector, limiting federal engagement and guidance on local development of recovery and resiliency plans after disasters. In 2017, the National Academies of Sciences, Engineering, and Medicine recommended that the biomedical research sector be included as a sub-sector under the Healthcare and Public Health Critical Infrastructure Sector.(38, 39) The roadmap action encompasses this recommendation and includes other biological sciences and biotechnology fields that may fall outside the biomedical research scope.

The *federal and local stakeholders* that, based on their organizations' missions and other responsibilities, may be responsible for implementing policies in accordance with these actions are included in Figure 6. Stakeholders from several federal agencies and local entities are responsible for implementing some aspect of the first five actions. Some of these stakeholders are responsible for implementing activities that are similar to biosecurity or biodefense activities, but are not considered part of these initiatives. Examples include policies for occupational health and safety and Biosafety in Microbiological and Biomedical Laboratory (BMBL), which is used to inspect laboratories approved for BSAT. Coordination and communication among government agencies and non-governmental stakeholders is crucial for successful implementation of policies developed based on these actions.

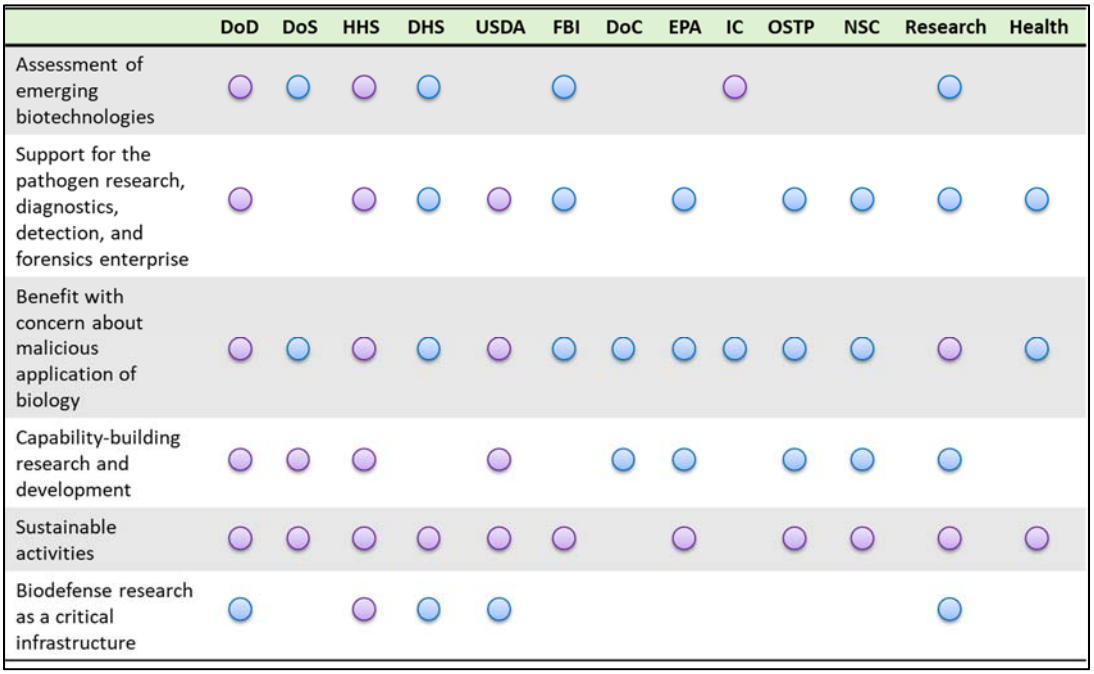

Figure 6. U.S. government and local stakeholders that may implement policies developed for each of the actions. The blue bubbles indicate responsibility of specific federal or local stakeholders for each of the roadmap actions. The purple bubbles indicate stakeholders who may have leadership roles in implementing the corresponding roadmap action.

DoD-Specific Roadmap

The Department of Defense supports a variety of science and technology activities assessing, preventing, detecting, and responding to natural, accidental, and deliberate biological incidents. Its programs span military health, research and development by the services and broader DoD, intelligence, CBRN (chemical, biological, radiological, and nuclear) homeland response,(40) outbreak response,(41) and CBRN threat reduction. Several of these DoD agencies overlap in their roles in biodefense and biosecurity. For example, the Defense Threat Reduction Agency (DTRA) supports research in chemical and biological defense to develop technological capabilities for detection and biosurveillance, early warning, medical countermeasures, and diagnostics.(42) DTRA works with other DoD entities, such as the United States Army Medical Research Institute of Infectious Disease (USAMRIID), which conducts basic and applied biodefense research.(43) DTRA also supports a variety of threat reduction activities, including global health security and cooperative biological engagement. Other DoD entities also engage in epidemic surveillance activities to gain awareness of potential biological threats.(44) Still others support research and development in biology to enhance military capabilities and to prevent harmful consequences of biotechnology.(30, 45-47) The DoD research enterprise that supports basic, applied, and translational research for any of these activities includes agency-level regulations for biosafety, biosecurity, and ethical treatment of human and animal subjects. These biodefense and biosecurity efforts enable DoD to meet its mission to safeguard the U.S. and its allies from biological threats by enhancing capabilities for threat awareness, prevention, and research and development for preparedness and response.(48)

Given DoD's role in implementing biodefense and biosecurity policies more broadly, several of the actions included in the stakeholder-wide roadmap apply to DoD. Figure 7 highlights the roadmap steps that most closely align with DoD mission areas of: threat assessment, threat prevention, research and development for biosurveillance and medical countermeasures, and response. Implementation of the steps highlighted in Figure 7, in coordination with the other responsible stakeholders (See Figure 6) could enable greater success in harnessing the capabilities and knowledge generated by science and technology advances and in reducing risk of theft, diversion, and deliberate malicious use of biology and biotechnologies.

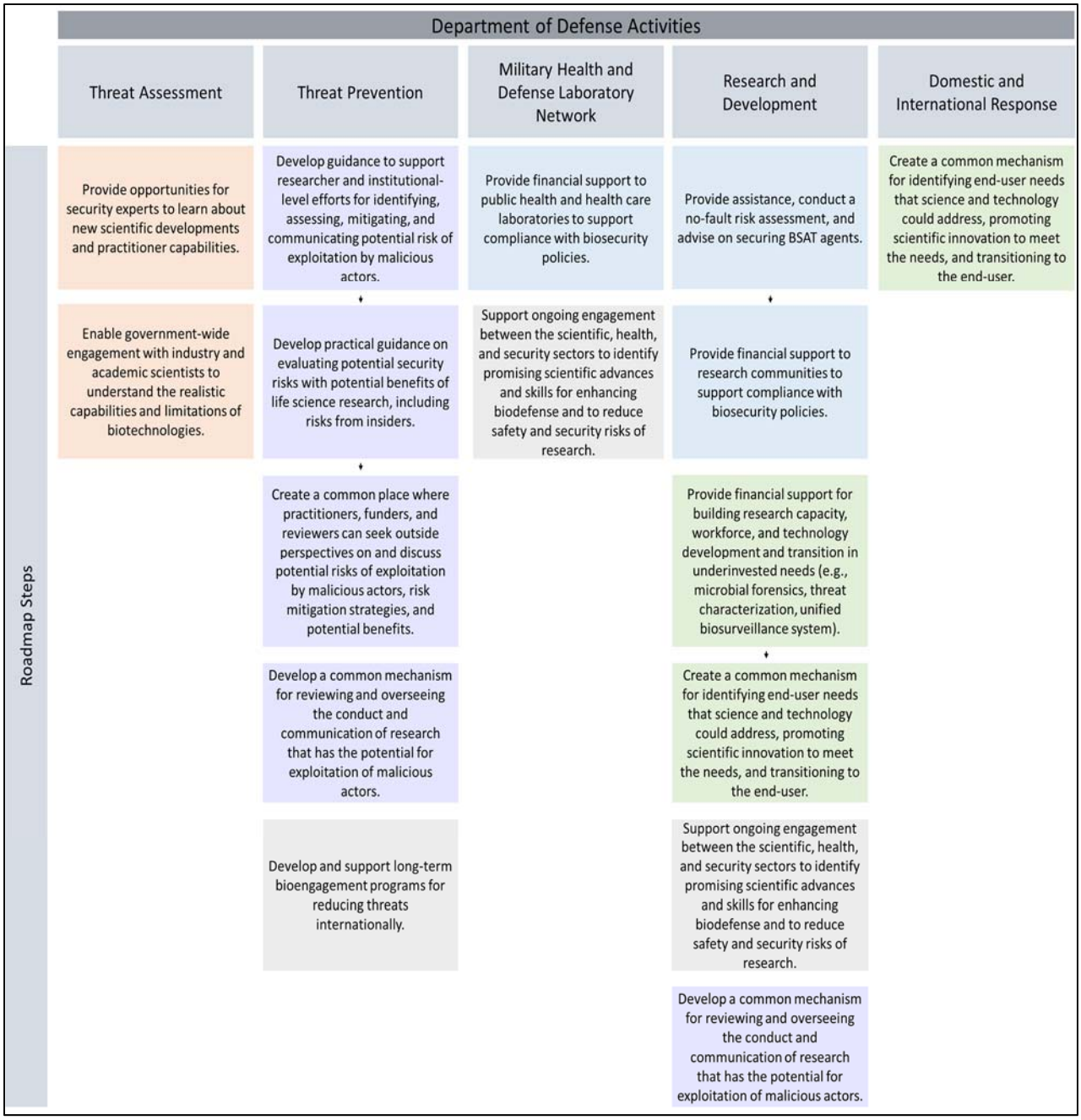

Figure 7. The steps in which DoD plays a leadership role. These steps are color coded with the six actions described in the broader roadmap and mapped to specific DoD biodefense missions.

Conclusions

The U.S. policy landscape for countering biological threats is split into two main groups: 1) biosecurity, which specifically focuses on preventing theft, diversion, or deliberate malicious use of biological sciences knowledge, skills, and technologies to cause harm; and 2) biodefense, which involves the development of capabilities and knowledge-based to assess, detect and monitor, treat (or vaccinate against), and respond to biological

threats. These two groups often affect the same stakeholders, which may result in mutual benefits among defense-oriented policies or present barriers to achieving either defense or security objectives. At the same time, the biotechnology landscape is changing dramatically, simultaneously presenting new opportunities for building technological capabilities and for enhancing security vulnerabilities. The policy analysis undertaken to inform this roadmap involved a systematic evaluation of existing policies for harnessing new advances in the biological sciences and biotechnology and for preventing malicious or accidental harms caused by pathogens, toxins, and scientific advances. This systems-based approach allowed for the identification of limitations and gaps in the current policy landscape, including those emerging from federal and local-level implementation. In addition, this analysis highlighted clear steps that could be undertaken by U.S. government, academic, and human, animal, and plant health stakeholders to address the critical limitations and gaps identified.

As new policies for biosecurity and biodefense are developed, their success and costs of implementation likely will be evaluated. To date, few evaluation metrics have been developed for evaluation of biosecurity and biodefense policy implementation. Those measures that have focused on quantitative or prescriptive assessments of required or recommended activities, such as the number of individuals trained in a course or the presence of locks on doors. Few have incorporated measures for evaluating achievement of program outcomes. For example, in 2015, the DTRA Cooperative Biological Engagement Program commissioned the development of metrics with which to evaluate its bioengagement activities. The final product included several activity and outcome-based metrics for assessing achievement of specific bioengagement activities. We have adapted this, and other similar, approaches to the evaluation of policies (See Evaluation Metrics Framework chapter). Using this framework, policy-makers and other stakeholders can begin to identify the types of data needed to evaluate the successful implementation of activities and the degree to which program outcomes or goals have been achieved.

A crucial determinant of success of a given policy is the feasibility of stakeholder implementation and potential downstream consequences. The U.S. government has two primary ways of calculating costs of new policies, both of which rely on economic data. The first involves the Congressional Budget Office estimates the costs of new legal mandates to governmental and non-governmental stakeholders.(49) The second involves regulatory agency review of the expected direct financial costs of implementing specified activities of a new or revised regulation. Neither of these assesses potential indirect costs to research, workforce, or any other intangible parameter or potential trade-offs that implementing stakeholders may make to off-set the direct costs. These indirect costs have downstream consequences to achievement of policy objectives. Some universities and researchers have calculated the direct financial costs of compliance to federal regulations. To the best of our knowledge, we are not aware of any analysis that has attempted to measure direct, indirect, and opportunity costs of policies. Therefore, we have developed an opportunity cost analysis that includes parameters for assessing each of these costs. The goal of this framework is to help policy-makers and other stakeholders identify the types of data needed to assess direct and indirect costs of a new

policy and the downstream consequences resulting from the indirect costs. Calculating these costs is important for determining the burden of implementing new measures and its potential effects on the advancement and application of research.

The roadmap, evaluation analysis framework, and opportunity cost framework described in this report seek to harness science and technology advances while simultaneously minimizing risk.

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