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# Democratizing Synthetic Biology

BALANCING BIOSECURITY, BIOSAFETY, AND CITIZEN  
SCIENCE

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## Executive Summary

Synthetic biology, the design and construction of biological systems and entities, is a growing field that combines a variety of disciplines, including molecular and cellular biology, bioinformatics, engineering, and genetics. The findings, tools, and techniques encapsulated by synthetic biology can be used for a variety of applications in health, energy, and the environment. For instance, researchers can design and build microorganisms (i.e. non-pathogenic *E. coli*, yeast, etc.) that produce pharmaceuticals; polymers for plastics, fabrics, and other materials; environmentally friendly biofuels to meet the world’s energy demand; and much more. As this field grows, even members of the general public have become empowered to use the methods and tools of synthetic biology to take on some of society’s greatest challenges.

The R&D cycle for synthetic biology can be broken down into three major parts: Design, Build, and Test. In the Design phase, a researcher will design DNA—the computer code equivalent for living systems—that contains instructions for a function an organism’s cellular machinery can execute. In the Build phase, researchers will make or obtain their designed DNA and then place it into a microorganism or other cell, sometimes using some form of genetic editing. Lastly, in the Test phase, the researcher has to determine if the cell is actually reading the inserted DNA and executing the desired function.

The R&D and manufacturing processes for synthetic biology have all been greatly expedited and improved over the last twenty years. Due to such advancements, many of the techniques and processes used in synthetic biology R&D have become accessible to everyday members of the public, enabling them to conduct their own synthetic biology experiments. Information on how to utilize the techniques and tools of synthetic biology—genetic editing, DNA design, etc.—are also widely available online across a host of free platforms. These advancements in technology and information-exchange have led to increasing democratization of synthetic biology in the United States. Democratization is defined as “the process of making something accessible to everyone” (Oxford Dictionary, 2018). One movement in particular, Do-It-Yourself Biology (DIYbio), is invested in furthering the democratization of synthetic biology. DIYbio is a decentralized movement of members, ranging from high school biology students to PhD scientists, that seek to learn more about synthetic biology and even conduct their own synthetic biology projects outside of an institutional or industrial laboratory setting. The movement has developed a Code of Ethics, collated resources online on safety and best practices, and created community laboratories where members of the public can work on synthetic biology projects under the direction of experts in the field. Many of these projects—conducted by everyday citizens—are quite groundbreaking, with potential applications ranging from pollutant remediation to generic pharmaceutical development.

However, members of academia, government, and the media have raised concerns that methods of synthetic biology could be misused by the public, DIYbio, or a nefarious actor, leading to purposeful or accidental harm to human health and the environment. There have been calls for stricter regulation on the information and tools that are available to the public, as well as calls for increased regulation of DIYbio. The following report will aim to detail DIYbio, review the concerns of stakeholders with respect to bioterrorism and bioerror,<sup>1</sup> and provide recommendations to improve US biosecurity and biosafety that do not hamper further democratization of synthetic biology. Specifically, this report will analyze three concerns regarding open-access information

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<sup>1</sup> Bioerror is a mistake made in biological sciences R&D that poses a threat to the environment and human health.

on synthetic biology and DNA sequence data, DNA synthesis of pathogenic or harmful sequences, and genetic editing technology for unethical and potentially dangerous purposes. The recommendations presented in Section 4 of the report are also summarized below:

### **1. Public Use of Synthetic Biology and Licensing or Registration**

- 1.1 Continue with no regulations on members of the public that practice synthetic biology outside of an academic or institutional laboratory setting.
- 1.2 The Department of Homeland Security, Department of Defense, or National Institutes of Health (NIH) should employ the National Academies of Sciences to prepare a detailed report on implementing a licensing and registration system for practitioners of synthetic biology.
- 1.3 The American Institute of Chemical Engineers (AIChE) should prepare trainings for the lay public on biosafety, bioethics, and best practices in synthetic biology and genetic editing.

### **2. Databases, Repositories, and Open-Access Information**

- 2.1 Continue with no regulation of databases, repositories, and other sources of open-access information for the time being. The Federal Bureau of Investigation Weapons of Mass Destruction Directorate and the Department of Homeland Security should continue to foster relationships with developers of repositories and databases to develop best practices that do not restrict access to information and promote responsible use of these platforms.

### **3. Commercial and Private DNA Synthesis and Screening Technologies**

- 3.1 The federal government should continue to fund research programs to develop next generation DNA screening technologies for use by the industry as well as law enforcement.
- 3.2 The State Department should work in conjunction with representatives of the Intelligence Advanced Research Projects Activity (IARPA) project titled Functional Genomic and Computational Assessment of Threats (Fun GCAT) to begin conversations at meetings of the Biological Weapons Convention on defining an international authority to implement such technology and monitor updates to select agent lists and databases.
- 3.3 Congress should appropriate \$500,000 to the Centers for Disease Control and Prevention (CDC) to conduct annual horizon scan studies of DNA printer technology and provide recommendations to the United States Department of Agriculture (USDA), State Department, and the Department of Health and Human Services (HHS) on regulating the raw materials used in these processes.

### **4. CRISPR Gene Editing Technology**

- 4.1 In the Department of Labor, Health and Human Services, and Education, and Related Agencies Act for Fiscal Year 2020, Congress should appropriate \$1 million to the CDC to work with the Animal and Plant Health Inspection Service (APHIS), Department of Defense, Department of Commerce, and NIH to review new pathogens and cell-types that could easily be weaponized or used for unethical purposes by genetic editing technology. The review should provide recommendations for updates to be made to the Federal Select Agents List. The review should also provide estimates on the costs to regulate and control the recommended additions to the list.

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## Abbreviations

<b>AIChE</b> American Institute of Chemical Engineers
<b>APHIS</b> Animal and Plant Health Inspection Service
<b>BSL</b> Biosafety Level
<b>BUGSS</b> Baltimore Underground Science Space
<b>CAS9</b> CRISPR Associated Protein 9
<b>CDC</b> Centers for Disease Control and Prevention
<b>CRISPR</b> Clustered Regularly Interspaced Short Palindromic Repeats
<b>DARPA</b> Defense Advanced Research Projects Agency
<b>DBT</b> Design-Build-Test
<b>DHS</b> Department of Homeland Security
<b>DIY</b> Do-It-Yourself
<b>DIYbio</b> Do-It-Yourself Biology
<b>DNA</b> Deoxyribonucleic Acid
<b>DOD</b> Department of Defense
<b>ds</b> double-stranded
<b>DURC</b> Dual-Use Research of Concern
<b>FBI</b> Federal Bureau of Investigation
<b>FELIX</b> Finding Engineering-Linked Indicators
<b>Fun GCAT</b> Functional Genomic and Computational Assessment of Threats
<b>GE</b> Genetic Engineering
<b>HHS</b> Department of Health and Human Services
<b>IARPA</b> Intelligence Advanced Research Projects Activity
<b>IGSC</b> International Gene Synthesis Consortium
<b>NIH</b> National Institutes of Health
<b>PPE</b> Personal Protective Equipment
<b>R&amp;D</b> Research and Development
<b>S&amp;T</b> Science and Technology
<b>ss</b> single-stranded
<b>USDA</b> United States Department of Agriculture
<b>WISE</b> Washington Internship for Students of Engineering
<b>WMD</b> Weapons of Mass Destruction

## Preface

### About WISE

The Washington Internships for Students of Engineering was founded in 1980 through the collaborative efforts of multiple professional engineering societies and the generous funding of the National Science Foundation. The program has since become self-sustaining, with many of the original societies supporting the program's operation. The program is designed to introduce students with an engineering background to public policy with the goal of developing young leaders that are mindful of how science and technology relate to society and government. During the nine-week program, students work on a policy paper on topics that interest them. They are also required to present their findings at the end of the program.

### About the Author

Ishaan Dev is a rising Senior at the University of California, Berkeley, studying Chemical and Biomolecular Engineering. Ishaan spent two years working in the Jay Keasling Laboratory on projects that aimed to engineer the isoprenoid and fatty acid pathways in yeast cells for the creation of useful biofuels and pharmaceuticals under the direction of Post-Doctoral Fellow Leo d'Espaux. During his time at the Joint BioEnergy Institute, Ishaan also conducted an Honors Thesis on the production of methyl ketones, a potential biofuel alternative, in yeast. Ishaan has also been active in the Engineers Without Borders (EWB): UC Berkeley Student Chapter, where he served as President from 2017 to 2018. EWB Berkeley focuses on implementing sustainable solutions to provide access to clean water and sanitation for communities in Peru, Panama, and Nicaragua. Ishaan is interested in the intersection of synthetic biology, health, and business. He hopes to expand upon these interests in graduate school.

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# 1. Introduction

In his *Notes on the State of Virginia*, Thomas Jefferson suggests that Americans should look to their own land for a way to prosper and contribute to industry instead of laboring for a manufacturer. At the time, productive property in manufacturing was only held by the few but was upheld by the labors of the many (T. Jefferson, 1787). Jefferson believed in a democracy in which citizens could all have relatively equal access to property and the means of production, which—back then—was fertile soil (Hardt, 2018). As industry plays a significant role in a capitalist democracy and its economy, allowing productive property to fall into the hands of the few could challenge the foundations of a democracy said to be owned by all of its people. Thus, democratizing the means of production returns the prospect of industry to all members of the public.

The thriving industries in the United States have transformed since its founding, with the advent of personal computing, improvements to health and medicine, and developments across many scientific fields. As Dr. Drew Endy of Stanford University remarks in his interview with Medium, Jefferson’s philosophies are in need of an update to capture the “means of production for the 21<sup>st</sup> century” (Duncan, 2018). The personal computing revolution that started in Silicon Valley is an excellent example of the democratization of the means of production in today’s world. Now, almost anyone can strive to create the next computer, software, or application as the means and know-how are shared open-source across many platforms. More recently, products of biotechnology have become increasingly important to the US economy, with domestic US revenues in the biotech sector exceeding \$320 billion—greater than 2% of the US GDP (Flores Bueso & Tangney, 2017). Aggregate revenues for the sector have grown over 10% annually in the last decade. This increasing relevance to the national and global economy has led to the emergence of the “bioeconomy,” the set of economic activities relating to the invention, development, production, and use of biological products and processes (OECD, 2018). Synthetic biology—the design and construction of new biological entities or redesign of existing ones—is exceptionally important to the research, development, and scaling of biotechnology products (EBRC, 2018). Between 2005 and 2015, the United States spent between \$500 million and \$1 billion dollars to fund synthetic biology research and development (Si & Zhao, 2016). Private and public biotech markets have also blossomed, with 224 new companies launching between 2013 and 2017 in public markets with initial public offerings totaling \$95 billion (Flores Bueso & Tangney, 2017).

Viewing the bioeconomy from Jefferson’s perspectives on democracy and industry, synthetic biology encompasses the means of production for the biotechnology industry. Just as was the case in the personal computing industry, there have already been leaps and bounds made to democratize synthetic biology—its findings, techniques, and tools—to allow Americans everywhere to have access and passage to products of biotechnology and this booming industry. One of the biggest movements on this front is the Do-It-Yourself Biology (DIYbio) movement. DIYbio is founded on the principles that “biotechnology and greater public understanding about it has the potential to benefit everyone” (Bobe & Cowell, 2008). Although it started off as just a public forum to discuss synthetic biology and biotechnology for scientists, students, and enthusiasts, DIYbio has grown to include entire community-led laboratories, where nearly anyone can come to learn about synthetic biology. DIYbio is completely decentralized. Each person who practices DIYbio (DIYers) and each community laboratory develop a unique set of their own experiments and procedures. A central part of the DIY movement is the Code of Ethics—a

document DIYers created, commented, and agreed upon (Bobe & Cowell, 2008). These ethics have fostered an environment of safe practice, transparency, and innovation in citizen science and DIYbio communities. However, DIYbio and the future of democratized synthetic biology are challenged by concerns over biosecurity and biosafety.

For the past century, there has been great concern by government and the general public that a biological weapon could be created by bad actors to inflict harm on large populations of people through methods encompassed by synthetic biology. Biological and chemical weapons attacks like the 1995 Tokyo subway sarin attack, the American Anthrax attacks, and the foiled ricin bomb attack in Germany combined with the creation of a synthetic horsepox virus by researchers at the University of Alberta have led to increasing fears over biosecurity and biodefense preparedness (Kupferschmidt, 2017). Media outlets have suggested the DIYbio community and the open-access synthetic biology resources it seeks to provide to the public only increase the inevitability of a biological weapons attack from a bad actor (Landrain, Meyer, Perez, & Sussan, 2013).

Due to this concern, members of the academic community, the media, DIYbio, and government have been torn on the issue of the path forward for further democratization of synthetic biology. George Church, Professor of Genetics at Harvard University, has suggested that “anyone who does synthetic biology should be under surveillance, and anyone who does it without a license should be suspect” (Baumgaertner, 2018). Other members of the academic community are less concerned about DIYers producing a biological weapon through methods of synthetic biology, suggesting that the technological and knowledge barriers are still too significant and would require a great deal of capital. There are also concerns of bioerror—accidental release of experimental materials and modified organisms into the environment that could be potentially harmful to flora and fauna (Cai et al., 2015).

The DIYbio community has worked hard to promote safety and good practices. Community laboratories have done tremendous good for the community, creating centers for individual DIYers to come to seek expertise and guidance on synthetic biology experiments in a safe, innovative, and controlled environment. The democratization of synthetic biology has empowered everyday citizens to take on some of society’s toughest challenges. For instance, Counter Culture Laboratories in California is working on a process to make open-access insulin, while Genspace in Brooklyn, New York is working on pollutant remediation using mushrooms (GENSPACE, 2018; Open Insulin, 2018).

The way forward for further democratization of synthetic biology and the DIYbio community is a trying one. Opposing views on DIYbio, whether it be praise for its revolutionary approach to citizen science or concerns over biosecurity and biosafety, are both not unfounded. It is necessary to tease apart both arguments, understand the concerns of key stakeholders, and present a way forward that encompasses the best interests of academia, industry, democracy, and public safety. The following report will analyze the three concerns listed below and provide recommendations for improvements to US biosecurity, biodefense, and biosafety that do not hamper continued democratization of synthetic biology.

1. Concern that open-access information relating to synthetic biology could provide pathogenic sequence data or instructions on how to create a potentially harmful product to human health.
2. Concern that a bad actor or reckless researcher will be able to actually obtain DNA that could code for a pathogen or other harmful product.
3. Concern that new genetic editing technology could be used for unethical and potentially dangerous purposes.

## 2. Background

### 2.1 Synthetic Biology

#### 2.1.1 Overview

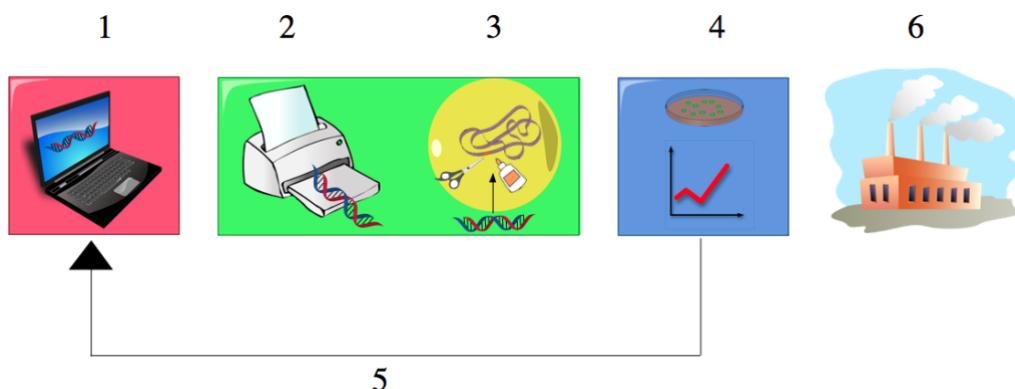
Synthetic biology, as defined by the Department of Health and Human Services, “is the developing interdisciplinary field that focuses on both the design and fabrication of novel biological components and systems as well as the re-design and fabrication of existing biological systems” (Department of Health and Human Services, 2011). Simply put, synthetic biology is the construction or modification of an organism in order to elicit a useful function. By harnessing the existing machinery and processes in living cells, scientists have been able to create gene and cell therapies, develop biosensors, and produce a multitude of useful products, from intricate biopharmaceuticals to next-generation biofuels. Techniques in synthetic biology—genetic editing, genetic recombination, etc.—are aimed at re-writing the genetic blueprints, DNA, of a cell. The edited DNA will instruct the cell to create desired proteins, structures or chemicals. A sequence of DNA that codes for a particular function in the cell is called a gene.

Synthetic biology was founded at the turn of the 21<sup>st</sup> century but has roots that trace back to the discovery of the *lac operon* by Francois Jacob and Jacques Monod in 1961 (Cameron, Bashor, & Collins, 2014) . The operon, a collection or circuit of genes in a cell, was found to respond to the cell’s environment and regulate feeding habits accordingly. From here, scientists began to develop their own gene circuits to elicit desired functions from cells. Synthetic biology efforts can lead to easier and cheaper methods of producing chemicals compared to time-

consuming plant breeding or expensive organic chemical synthesis. Some notable examples include: engineering non-pathogenic *E. coli* to produce insulin for treatment of diabetes and engineering yeast to aid in the production of artemisinin for treatment of malaria (Fraser, 2016; Ro et al., 2006).

The field of synthetic biology has grown since the early 2000s. Some applications include re-creating or enhancing pathogenic viruses and bacteria for the creation of advanced cures, manufacturing chemicals by exploiting or building metabolic pathways, and modifying the human microbiome, immune system, and genome to confer therapeutic benefits. However, beneficial applications are many times enabled through research that could be potentially used to cause harm, also known as Dual-Use Research of Concern (DURC). For instance, in attempting to create anticipatory cures for viruses, researchers may purposefully enhance the properties of a certain virus to understand how it behaves and operates. The data is of course useful for designing curative measures, but the laboratory viruses created could pose a potential health and safety risk if obtained or even recreated by the wrong people. Although this is more a critique of how such research is conducted, methods of synthetic biology are many times employed in DURC and fall subject to similar concerns.

### 2.1.2 The Process



**Figure 1 Process Diagram:** The general process of synthetic biology is outlined in section 2.1.2. The boxes in color reflect phases of the Design-Build-Test Cycle. Red boxes designate the Design phase. Green boxes designate the Build phase. Blue boxes designate the Test phase. Step 1 depicts designing a DNA construct (Vespa, 2011). Step 2 is synthesizing DNA to be used in step 3 (B. 2014), adding DNA to a cell (Glue Clipart, 2017). Step 4 is where the researcher will test the cell to see if it elicits the desired function (Itzuri, 2015). If the cell does not do the desired function, the researcher must learn from his mistakes and return to step 1, represented by step 5. If the cell elicits the function successfully, the researcher may move on to step 6, scaling, manufacturing, or applying their design for use (Career Guru, n.d.).

Synthetic Biology and principles of genetic engineering can be applied to many applications. Although there are intricacies to each R&D effort or application, the general process of synthetic biology is depicted above in **Figure 1** and is described below.

1. **Design:** The first step is to turn an idea into a construct or gene circuit, which will code for the proteins that one wishes the cell to make. Genes are parts of an organism's genetic code. Each of these parts will tell the cell to do a specific function. A gene circuit or gene construct is a set of genes. There is software to help researchers design these constructs and optimize them for use in a host cell. A host cell refers to the organism whose DNA will be edited by the researcher.

2. **Build: DNA Synthesis:** DNA is the blueprint that will tell the cell what to make. The gene circuit designed in step 1 will be synthesized using a DNA or gene synthesis machine that the researcher has or by a third-party gene synthesis company. Constructs that only require ubiquitous or easy to locate DNA sequences are also commonly created through methods of DNA cloning.
3. **Build: Delivery of DNA:** The researcher will then take the synthesized DNA and deliver it into the cell using one of many methods. Genetic editing is one such method for delivering DNA into a cell that has gained popularity in R&D. Researchers can employ genetic engineering techniques to transfer a desired gene construct into the genome of a host cell. In essence, the researcher provides the blueprints in the form of DNA. The cell provides the machinery and executes based on the blueprint.
4. **Test:** Once the DNA is planted in the cell, the cell is allowed time to recover and accept the change. To confirm the change has been accepted by the cell and is indeed correct, researchers will then undergo a process of screening. Finally, the cells are grown in a medium to multiply. Measurements are taken to determine if the cells are executing the desired function.
5. **Repeat:** As with any scientific endeavor, failure is to be expected. If a construct is not accepted by the cell or does not cause a desired change in cell function and performance, researchers will learn from their mistakes and return to step 1. As failure is quite common, steps one through five are commonly nicknamed the Design-Build-Test Cycle (DBT Cycle). The cycle is also referred to the Design, Build, Test, Learn Cycle, to highlight the great deal of learning a researcher must do to achieve success in this trial-and-error process. Here, the learning portion is implicit to the cycle.
6. **Scaling, Manufacturing, or Applying:** If one is trying to create a chemical, protein, or other product that needs to be produced in large quantities, researchers and companies will look to scale their productions to make them marketable. In other cases, developed biological entities will be prepared to be used in practice.

Each of the steps outlined above has its own challenges and barriers. The field has moved rapidly to remove these barriers and streamline processes. Just as the potential to create biotechnology focused on improving health, energy, and the environment will increase as barriers to synthetic biology fall, so too will the potential for a bad actor to create a product that challenges our nation's biosecurity. Currently, it takes weeks to months of time and expertise to create a successful product or even to complete a single experiment in a string of experiments. This time is decreasing dramatically with increased automation of the DBT Cycle and advancements in the field. The following sections will review the barriers involved with three integral steps in the process outlined above and how these barriers have degraded with the progression of the field of synthetic biology. Advancements in automation, the Testing phase of DBT, and the Scaling, Manufacturing, or Applying phase are not considered here in depth.

### 2.1.3 Design

One of the first steps in synthetic biology research is to design a gene construct that codes for a specific cellular function. Designing new gene circuits can sometimes be a guessing game. Researchers first have to determine or design the genes that will yield the outcomes they require. They have to then build and test their designs to confirm their hypotheses, as is the scientific way. This ongoing cycle is known as the Design-Build-Test Cycle and can be very costly to the

researcher in both time and money. Since the inception of synthetic biology, the DBT cycle has become exceptionally faster, but is still a large bottleneck to producing viable products. Companies like Ginkgo Bioworks are working on platforms that can test hundreds of different constructs in an organism at a time to see which is successful. These machines rapidly reduce the time to produce viable strains for synthetic biology projects (GINKGO BIOWORKS, 2016).

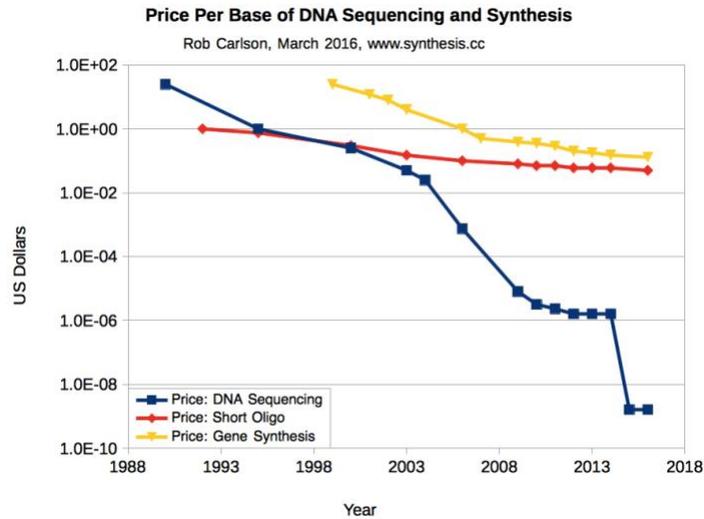
To aid in expediting the Design process of DBT, open-access repositories have been developed to allow researchers to share a variety of genes and synthetic biology parts. As repositories advance, researchers will be able to quickly and effectively mix-and-match gene sequences that have been tried and tested, streamlining R&D and innovations. The pioneering repository, the Registry of Standard Biological Parts, has been active since 2003 and is used primarily to provide synthetic biology or gene parts, coined BioBricks, for the Internationally Genetically Engineered Machine competition (iGEM). The registered parts are screened by a commercial partner to ensure they are safe and do not pose a security issue (iGEM FOUNDATION, 2017). The Registry of Standard Biological Parts does distribute parts once a year to academics and non-profits. The BioBricks Foundation is developing BioNet, a free biological inventory system and browser which will help researchers keep track of their stored biological parts and determine if other laboratories or researchers have parts that may be of use to them. There are other repositories for synthetic biology designs and constructs, like SynBioHub, JBEI-ICE, and SBOL Stack (McLaughlin et al., 2018). The National Institutes of Health operate one of the largest databases of DNA sequences in the world, Genbank. Genbank has made it exceptionally easy for researchers to obtain sequence data, streamlining research (NCBI, 2017). Genbank also has sequence data on pathogens.

#### 2.1.4 DNA Synthesis

Once researchers design a gene construct, they have to then find the parts or synthesize them and put them into a cell.<sup>2</sup> Genes can be artificially synthesized using a DNA printer or synthesizer. Reliable and quick DNA synthesis is absolutely imperative to the DBT process of synthetic biology, especially if a researcher is using a gene that does not exist in nature or is not easily obtained by other means. The cost of synthesizing a strand of DNA or gene has decreased by more than 100-fold between 2000 and now (**Figure 2**) (Carlson, 2014). The cost to sequence DNA constructs has decreased exponentially during the same time period, allowing researchers to test the inserted DNA in an organism for accuracy. The leaps made toward cheaper DNA synthesis reduce economic burdens on laboratories and allow researchers to build and test more of their designs.

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<sup>2</sup> DNA amplification is the process of taking one copy of a strand of DNA or gene part that may exist in the genome of an organism and then producing many copies of that part through PCR amplification or cloning. These gene parts can now be used in the Build phase of DBT. If the gene cannot be obtained easily, researchers will then look to chemically synthesize the DNA.



**Figure 2 Rob Carlson Curve:** The Rob Carlson Curve is commonly used to track the cost of sequencing and synthesizing DNA. The cost of synthesizing genes has fallen over 100-fold in the last 15 years (Carlson, 2016).

Most laboratories order their genes from a commercial DNA or gene synthesis company. Many of these companies follow recommended screening processes. Screening orders is important to ensure customers are not ordering DNA that could be used to produce a pathogen or aid in the creation of a toxin or other harmful product. Screening processes and standards for DNA synthesis started in 2009 with the creation of the International Gene Synthesis Consortium (IGSC) (<https://genesynthesisconsortium.org/>). The IGSC was started by companies in the DNA synthesis industry to develop voluntary protocols for individual synthesis companies to screen DNA sequence orders and verify customers. Members of the IGSC are from all over the world and hold 80% of the global DNA synthesis market (DiEuliis, Carter, & Gronvall, 2017). IGSC screening protocols call for companies to screen orders against multiple databases including the US Federal Select Agent list, Australia Group list agents, controlled sequences in the U.S. Commerce Control List, and European Union sequences list. Following the creation of the IGSC, the Department of Human and Health Services created *Guidance* to provide US gene synthesis companies with recommendations for screening orders and customers. The *Guidance* calls for providers to screen orders for compliance with the agent lists provided by Select Agent Regulations and the Export Administration Regulations' Commerce Control List (DiEuliis et al., 2017). *Guidance* recommends customers be screened against lists of “denied or blocked persons and lists maintained by the Departments of Commerce, State, and Treasury” (Department of Health and Human Services, 2011). *Guidance* provides recommendations for industry but does not mandate compliance.

DNA synthesis machines are also available to members of the public. The cost of maintaining and operating these machines is decreasing but is still quite significant. These machines can be operated from the privacy of someone’s residence. There is now increasing concerns on the potential for bad actors to use these machines to create harmful sequences. Laboratories normally prefer to send orders out to a gene synthesis company for highest efficiencies and best prices. Gene synthesis companies’ business models are entirely focused on efficient DNA synthesis and sequencing. Laboratories working on projects outside of DNA synthesis do not look to spend the time and money to ensure an in-house synthesizer is operating at maximal efficiency.

To aid in further democratization of synthetic biology, the Free Genes Project by the BioBricks Foundation aims to provide free genes to the public (BioBricks FOUNDATION, 2017). The project openly asks for recommendations of genes or DNA sequences that should be freely available to the public. The project will provide these parts to individuals for free. The project has screening processes to mitigate concerns related to pathogenic or harmful sequences mentioned briefly. Orders to the Free Genes Project are completely public and can be reviewed or commented on by anyone.

### 2.1.5 Gene Editing Technology

“Build” in DBT sometimes requires the use of genetic engineering—the process of modifying an organism’s genome. Once a gene construct is synthesized, a gene editing technique can be used to forcefully add the construct to a host organism or to the host organism’s genome.<sup>3,4</sup> The cell reads its genomic DNA to carry out functions. There are many methods to conduct edits to the genome. Enzymes, proteins in a cell that facilitate a chemical operation, called nucleases are commonly used to cut genomic DNA to allow for the insertion of donor DNA. These nucleases can also be used to remove genes in the genome that provide the cell a function that is counterproductive to the goals of the researcher. The big three nucleases used for gene editing are named Zinc Finger Nucleases (ZFNs), Transcription Activator Like Effector Nucleases (TALENs), and Clustered Regulatory Interspaced Short Palindromic Repeats Associated Protein 9 (CRISPR/CAS9)—the newest of the three. CRISPR/CAS9, commonly referred to as CRISPR, is a gene editing tool that can take donor DNA and cut-and-paste it into a host genome. The technology is lauded for its efficiency and ease-of-use.

CRISPR-CAS9 is an exceptionally powerful tool for research and can easily be used to genetically engineer organisms—including humans—for the purposes of gene therapy and germline editing. Of course, the use of CRISPR for these purposes has raised many ethical concerns and is the subject of much debate in the global scientific community. CRISPR is gaining traction in the DIYbio community. Community labs hold workshops on CRISPR editing. CRISPR proteins can also be bought online for less than \$200. Josiah Zayner, a visible figure in the DIYbio community,<sup>5</sup> has created a DIY Gene Engineering Kit for \$159 that includes the CRISPR editing system (ODIN, 2018). His company, Odin, carries a lot of DIY laboratory equipment.

### 2.1.6 Testing, Scaling, Manufacturing, or Applying

To confirm a cell has accepted donor DNA accurately, researchers may sequence parts of the host genome. The researcher then has to use methods of analytical chemistry to determine if and how well the design works in the host organism. If the researcher is attempting to produce a chemical product or molecule from the organism, they may need to scale their processes to produce a significant amount of the product for commercialization. Both testing methods and scaling

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<sup>3</sup> Host refers to the organism or cell that a researcher will be building. The DNA to be added to the host is called donor DNA.

<sup>4</sup> Researchers do not necessarily need to integrate a gene circuit into the host genome to obtain desired functionality. Some organisms can read genes on plasmids, circular gene fragments, that are floating around in the cell. Plasmids can be unstable over many cell divisions. Plasmids are great for providing proof of concept. To achieve a genetically edited microorganism that has stable functionality over long periods of time, researchers will most likely choose to integrate donor DNA into a cell’s genome.

<sup>5</sup> Josiah Zayner would fall into the category of “biohacker,” a subcategory of the DIYbio movement that has raised some concerns about the ethics of DIYers. Biohackers look to conduct experiments that can enhance their physical selves. Many use their own bodies as test subjects.

methods are the subject of a lot of research, including studies on next-generation sequencing and advanced manufacturing. Scaling a product requires a lot of fine-tuning of environmental conditions, cellular pathways, and equipment. Scaling is another barrier in synthetic biology and the creation of biotechnology but is not considered in depth in this report. Not all products require scaling. For instance, a gene therapy cure will require a downstream process that aims to improve the delivery mechanism of the treatment to a cell or organism requiring the therapy.

## 2.2 Do-It-Yourself Biology

### 2.2.1 Overview

A hallmark of the democratization of synthetic biology has been DIYbio. The Do-It-Yourself Biology movement—DIYbio for short—seeks to make synthetic biology technology and practices available to the general public outside of traditional academic or industrial settings (Grushkin, Kuiken, & Millet, 2013). The movement began in the early 2000's, when University of Washington Researcher, Rob Carlson, showcased how easily he could build an at home molecular biology laboratory (Carlson, 2005). At that point, the next garage-born phenomenon started gaining traction. Jason Bobe and Mackenzie Cowell launched DIYbio.org in 2008, an online forum for synthetic biology enthusiasts (Grushkin et al., 2013). The forums were used to set up meetings for amateur DIYers to test their skills at simple, high school level biology experiments. Members of the DIY community organized and were able to start community DIY laboratories, where members purchase a monthly subscription to practice synthetic biology. The first of these laboratories, Genspace, was started in New York in 2009. There are now over 50 DIY laboratories worldwide according to DIYbiosphere, a website that serves as an online database for DIY projects worldwide (DIYbiosphere, 2018). In 2011, delegates from these laboratories in Europe and North America met to create a framework of ethics for the DIYbio community. These codes ushered in the beginning of a decentralized governance for DIYbio that has served the community well. Since then, multiple DIYbio and biohacking conferences have been held to bring together members of the community to discuss projects and good practices.

DIYbio answers the call to democratize synthetic biology. The field and its applications will re-write the conversations we have regarding medicine, energy, and agriculture. Many, including Genspace Founder, Ellen Jorgensen, believe community laboratories provide the creative space to revolutionize synthetic biology in the same ways makerspaces, incubators, etc. continue to revolutionize the personal computing industry (Jorgensen, 2012). DIYbio is also practiced by individuals in their own homes.

The flagship forum and website for the DIYbio community, DIYbio.org, is designed to promote a vibrant and—more importantly—safe DIYbio culture. The website has an “Ask Biosafety Expert” option to provide DIYers answers to questions regarding lab safety and practice. The service is funded by a grant from the Woodrow Wilson International Center for Scholars (DIYbio.org, 2012). The website also helps individuals meet with other DIYers, read up on the DIYbio Code of Ethics, and review hot topics in the field. DIYbio.org also feeds into DIYbiosphere.org.

### 2.2.2 DIYbio Demographics

In 2013, the Woodrow Wilson International Center for Scholars surveyed members of the DIYbio community in an attempt to understand their backgrounds, interests, and views. 359 people responded to the survey that was posted on DIYbio.org, in community labs, and hackerspace

forums (Grushkin et al., 2013).<sup>6</sup> The survey captured about 10% of the DIYbio community in 2013. The findings are summarized below.

- 55% of respondents studied biology at a college level or higher. Less than 5% had no biology background whatsoever.
- 92% of DIYers work in group spaces. 8% of respondents worked exclusively from home.
- Only 6% of respondents work in BSL-2 laboratories.
- 40% of respondents built some of their own lab equipment.
- 57% of respondents believed that some government oversight would be required in the future. 75% believed no government oversight was needed at the time.
- 73% of respondents favored absolute or near absolute transparency between their work and the community. 6% favored absolute privacy.
- 28% of DIYers do some or all of their work in a government, academic, or corporate lab.

### 2.2.3 Community Laboratories

According to the 2013 survey conducted by the Wilson Institute, 92% of respondents work in a group setting. One such setting is the community lab space. The DIYbio community has successfully made Biosafety Level 1 (BSL-1) community laboratory spaces where they can practice amateur synthetic biology and genetic engineering. BSL-1 laboratories can work with non-pathogenic microorganisms like *E. coli* and yeast (CDC, 2009). The goal of these laboratories is primarily to democratize synthetic biology and educate members of the general public on the science. Some laboratories also look to promote entrepreneurship. Many of these laboratories are started in unconventional spaces like warehouses. Labs are owned and operated by completely different sets of entities and personnel. No two labs are the same, but there are some distinct similarities. For instance, to become a member of such a laboratory, one may have to pay a fee on a monthly or annual basis. When applying to become a member, most community labs also ask for a short application to understand an applicant's intentions in the lab. Members are anywhere from PhD scientists with significant experience all the way to amateurs with little background in the sciences. Labs provide workshops and training to teach members proper safety techniques and about new gene editing technology. Workshop topics can span anywhere from forensic analysis to bioprinting.<sup>7</sup>

### 2.2.4 Community Laboratory Funding

DIYbio labs are funded from a variety of sources. The largest source of revenue for many DIYbio labs are membership or course fees (Scheifele & Burkett, 2016). DIYbio labs like BioCurious in Santa Clara, CA charge monthly or annual fees for members to use the laboratory space. Genspace in Brooklyn, NY offers different membership plans depending on the capabilities and freedom a member desires. Labs also collect fees from educational workshops they hold.<sup>8</sup> Laboratories can be set up as 501(c)(3) non-profits to gain federal tax exemption, a sometimes-lengthy process facilitated by the Internal Revenue Service. Grants that are provided to DIYbio labs from philanthropic or other sources are commonly awarded to specific projects and are not

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<sup>6</sup> A hackerspace is a workspace where people with common interests, primarily in S&T, collaborate on ideas and projects.

<sup>7</sup> This paper will pull examples and reference a select number of DIYbio laboratories. As no two laboratories are the same, these examples cannot be used to create broad generalizations.

<sup>8</sup> Some educational workshops are free.

able to support the operating budget of the community lab (Scheifele & Burkett, 2016). When starting a DIYbio lab, founders have looked primarily to crowdfunding and private donations to develop a seed fund. Maintaining a reliable source of revenue is a struggle for many laboratories.

### 2.2.5 Community Laboratory Safety

The Code of Ethics developed by the DIYbio community in 2011 promotes safety and transparency. Most laboratories, including BioCurious and BUGSS, developed intricate safety protocols before opening their doors to the community to ensure proper practices. DIYbio labs also have a project review process where a committee—comprised of primarily senior-level lab officials holding advanced degrees—approves projects for lab members. The review process considers the intentions and safety of the project, microorganisms and reagents to be used, and qualifications of the investigator. Lab leadership (i.e. Directors, Managers, etc.) normally hold an advanced degree in a topic related to synthetic biology and have experience working in an institutional research laboratory.

DIYbio laboratories have their own safety guidelines and resources to ensure members conduct day-to-day work in a responsible manner (Burkett, 2012). These guidelines are quite similar to those found in labs at research institutions. Guidelines call for strict use of Personal Protective Equipment (PPE) and proper disposal practices of items from microorganisms to broken glass. Labs normally have a dedicated safety officer to ensure safe practices are followed and to answer questions that members pose. Generally, no microorganisms are allowed to leave these facilities to prevent environmental release. Labs also form relationships with emergency response groups and statutory authorities to ensure lawful compliance (Burkett, 2012). Furthermore, labs partner with a waste disposal company for proper disposal of biohazardous waste. BUGSS has implemented a “white list” of chemicals that are safe to use by inducted lab members (Burkett, 2012). Anything off this “white list” has to be approved by lab leadership. Many DIYbio labs also have safety trainings members are required to take. Safety practices are often integrated into workshops and events as well. Laboratory members are not allowed to do work without supervision by a lab manager, unless they have proven themselves capable of independent lab work through months of supervised work and facetime with laboratory personnel.

### 2.2.6 Law Enforcement and State Authorities

DIYbio community laboratories and institutional laboratories that practice synthetic biology have good relations with the Federal Bureau of Investigations (FBI). FBI Special Agents local to these community labs and normally seasoned in the Bureau’s Weapons of Mass Destruction Directorate help facilitate these relationships. The FBI talks frequently with community labs to see what projects they are working on and if they can provide any assistance. The FBI is interested in “safeguarding science” and has worked alongside the DIYbio community to create a “network of sources in the community to help detect possible threats” that could harm the public or the future of the DIYbio movement (Regalado, 2016). The FBI provides guidance to their DIYbio and institutional contacts on how to spot researchers or colleagues that may be conducting suspicious activities. Members of the FBI also attend conferences the DIYbio community holds (Regalado, 2016).

DIYbio laboratories, like Genspace, BioCurious, and BUGSS, also work with state authorities and first responders in their areas to ensure proper compliance with state laws and statutes (Burkett, 2012). Working with first responders is key to mitigating an emergency at one

of these laboratories in an appropriate and safe manner that is conscientious of the experiments and chemical or biological hazards that may be present.

### 2.2.7 Individual DIYers

A small fraction of the DIYbio community does work exclusively from home and not in any group setting. It is harder to say exactly how many individuals work by themselves on DIYbio projects as only 10% of the community responded in the 2013 survey, and the community is sure to have grown tremendously since then (Grushkin et al., 2013). Setting up an at home DIYbio laboratory is not as difficult now as it was in the early 2000s. There are now instruction manuals on how to economically create the necessary equipment for molecular biology experiments at home from everyday items one can pick up at the hardware store. In essence, these are DIY thermocyclers, centrifuges, gel electrophoresis machines, and so on. It is important to note that although a DIY piece of equipment works, efficiency is exceptionally important to the Design-Build-Test cycle. Equipment purchased from a manufacturer will have more consistent results and will lead to cleaner experiments. To genetically engineer a BSL-1 microorganism through the process outlined in section 2.1.2, an individual may spend \$1,000 on equipment alone. Odin, started by Josiah Zayner, sells their Genetic Engineering Home Lab Kit for just under \$2,000 (ODIN, 2018). The kit comes with everything one would need to start a beginner genetic engineering laboratory.

## 3. Findings and Key Concerns

### 3.1 Biosecurity

Members of academia, government, and the public fear that continued democratization of synthetic biology could lead to acts of bioterror or bioerror. Some individuals in these stakeholder categories have called for increased regulation of DIYbio and the tools and resources of synthetic biology. This narrative currently surrounding DIYbio and public practice of synthetic biology outside of a traditional laboratory setting is one of fear prompted primarily by the reactionary nature and gaps in United States biosecurity and biodefense.<sup>9,10</sup> Reactionary attempts to patch gaps in biosecurity and biodefense could be ineffective and overly restrictive on further attempts to democratize synthetic biology. To develop a way forward to safely and securely continue the democratization of synthetic biology, the following section will detail three concerns regarding open-access information, DNA synthesis, and gene editing. Section 3.1 will also detail how these concerns relate to current attempts to democratize synthetic biology. The three concerns are contextualized by phases of the DBT Cycle discussed earlier. These concerns will help illuminate potentially concerning gaps in biosecurity and biodefense. Section 4 will aim to provide recommendations that fill these gaps and mitigate concerns without hampering continued democratization of synthetic biology.

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<sup>9</sup> Biosecurity is the prevention of malicious use of biological sciences knowledge, skills, materials, and technologies to cause harm (Berger, Dieuliis, Meyer, & Rao, 2018).

<sup>10</sup> Biodefense involves the development of capabilities to assess, detect, monitor, respond to, and attribute biological threats (Berger et al., 2018).

### 3.1.1 Bioterrorist: A Possible Profile

Analyzing acts of extremism or terror in the last one-hundred years, one can quickly conclude these acts are committed by an individual or a group that has access to significant resources. According to the Wilson Institute study, 92% of DIYers surveyed in 2013 work in some sort of community space. The other 8% work exclusively from home. DIYbio community laboratories already have reviewal protocols for new projects and members to ensure safety. These laboratory leaders' close relationships with the FBI also help foster an environment of responsibility and accountability. More likely, the community will serve a larger role in reporting suspicious actors to aid in early detection and avoidance of a biological weapons attack. A recent National Academies of Sciences, Engineering, and Medicine report, *Biodefense in the Age of Synthetic Biology*, recommends the DOD and other national security agencies create “civilian infrastructure that informs population-based surveillance, identification, and notification of both natural and purposeful health threats” (Biodefense & Studies, 2018).

The NAS report on biodefense also suggests a biological weapons attack through synthetic biology efforts is not likely to come from an individual bad actor but from a group that has significant expertise in the field (Biodefense & Studies, 2018). Expertise in synthetic biology currently requires higher education. This profile for biological terrorists could change as knowledge and design barriers fall due to increasing availability of knowledge on synthetic biology processes, techniques, repositories, and information banks. Yet, a report conducted by Jefferson, Lentzos, and Marris makes a strong case for the need of tacit knowledge—years of experience working on projects in an institutional laboratory setting—in producing an advanced product of biotechnology like a bioweapon (C. Jefferson, Lentzos, & Marris, 2014). DIYbio community laboratories may now be able to provide tacit knowledge to an individual, but these laboratories have strict project reviewal processes, are committed to an environment of transparency and safety, and have direct connections to the FBI. These factors in mind, it would be quite impossible for a bad actor to work in one of these facilities without being reported.

### 3.1.2 Open-Access Information

As synthetic biology techniques and findings advance, the question arises whether or not all findings should be available open-access, especially pathogenic sequences. The Department of Homeland Security held a workshop with relevant stakeholders from academia, government, and industry in January of 2018 to discuss the future of genome sequence databases and their relevance to security (Spopescu, 2018). The proceedings of the workshop are not public. This is an important step in developing best practices for these databases. The Registry of Standard Biological Parts already screens sequences uploaded to the repository. JBEI-ICE Public asks users to provide information about themselves (i.e. name, email, “about you,” etc.) as well (Joint BioEnergy Institute, 2018).

Repositories are exceptionally important for expediting R&D in academic institutions and industry. Gene constructs that have certain functionality in a cell could be useful to another researcher's project. Researchers can search these platforms for previous constructs that worked successfully, so they do not have to start from scratch. The public has access to many of these repositories as well, fueling concerns that sequence information could be misused by members of the public, DIYbio community, or even academia and industry. The DIYbio community was founded on the principles of safety and transparency, as outlined in its Code of Ethics. Exploitation

of registries and databases for nefarious use could come from bad actors of any background. Regulating these databases is a nascent conversation.

### 3.1.3 DNA Synthesis

Knowledge barriers may fall as information on synthetic biology becomes easier to access and understand by the lay public. Currently, novel sequences and those that are more complex are chemically synthesized. Creating gene constructs with genes that are common in BSL-1 organisms can easily be done by a researcher in a laboratory setting using methods of DNA recombination and cloning. However, as DNA synthesis and sequencing become more affordable and efficient, researchers of the near future will obtain most of their gene constructs from a commercial entity or produce them using a personal DNA synthesis machine. There is concern in the biosecurity community that a bad actor or a reckless researcher could synthesize DNA for potentially harmful purposes, such as creating a virus, pathogenic bacteria, or other biohazard. Most academic institutions and DIYbio community laboratories obtain their synthesized DNA through a commercial DNA synthesis company.

There are many gaps in how DNA orders are screened by commercial suppliers that some believe could be exploited by nefarious actors. Many of these companies screen for known pathogenic and harmful DNA sequences across multiple select agent lists, as mentioned in Section 2.1.4. Lists have sequence data and names of pathogens, toxins, or agents that pose a high risk to human health. However, these lists are “static.” Lists are commonly updated once a new threat is assessed, which can be a lengthy process. These lists by no means capture all of the possible DNA sequences that could code for pathogens or help develop toxins (Julias, 2016). As technology and understanding in this sector advance rapidly, scientists with either malicious or non-malicious intent could modify an existing pathogenic sequence or create a pathogenic sequence that is not on any select agent list, avoiding flags during a screening process. To prevent such exploitation, there have been calls to create screening technology that is able to “recognize the genetic mechanisms of virulence” or pathogenicity and characterize novel sequences as harmful or benign (Garfinkel, Endy, Epstein, & Friedman, 2007).

Next, the *Guidance* set forth by the Department of Health and Human Services only calls for screening of double-stranded (ds) DNA of 200 base pairs (bp) or more (Department of Health and Human Services, 2011).<sup>11</sup> Small fragments of DNA (<200bp) may have overlap with both longer benign sequences and longer pathogenic sequences. Determining whether the fragment will be used for the creation of a pathogenic strand or a benign one is burdensome to a gene synthesis company. For these reasons, sequences under 200bp are not screened against databases of controlled substances. Researchers can also request several sequences that are smaller than 200 bp and then join them together in their laboratory at another time. Such a process of joining can be difficult to do with very long gene constructs, is prone to error, and can be time intensive. Recently, a research group from the University of Alberta re-constituted a horsepox virus by stitching together seven 30,000bp strands of DNA obtained from GeneArt, a mail-order DNA synthesis company (Noyce, Lederman, & Evans, 2018). Since the research group was affiliated with an academic institution, GeneArt did not have cause for alarm. Re-constituting the horsepox virus is said to have costed nearly \$100,000 and used advanced laboratory equipment (Kupferschmidt, 2017). Trying to re-create the virus from over 1000 pieces of DNA that are less than 200bp would

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<sup>11</sup> A strand of DNA is made up of many units called base pairs.

be hard for someone not affiliated with a recognized institution to do without raising suspicion. It would also be a serious undertaking, requiring tacit knowledge, expertise, capital, and time.

Additionally, scientists are now able to synthesize DNA and whole genomes using single-stranded (ss) oligonucleotides (DiEuliis et al., 2017). The *Guidance* only provides recommendations for dsDNA synthesis of sequences greater than 200bp. Developing a full pathogenic sequence from ss-oligonucleotides could be an avenue used by nefarious actors.

Although there are a number of gene synthesis companies that do not follow the HHS *Guidance* or are not members of the IGSC, there are high barriers for bad actors to obtain synthesized DNA from commercial sources today due to this widespread use of sequence and customer screening. DIYbio community laboratories, specifically BUGSS, add an additional level of screening, where a safety committee in the laboratory will review sequences that are commercially synthesized to ensure DIYers are adhering to safe practices. As synthetic genomics technology progresses rapidly and knowledge barriers diminish, it is important to remain anticipatory in commercial screening practices without relying on direct government intervention that could be costly to legitimate and non-malicious researchers. Intelligence Advanced Research Projects Activity (IARPA) has anticipated the need for next-generation DNA sequencing and screening technologies to serve as countermeasures toward nefarious actions and accidents that are likely due to the “democratization of biotechnology” (Julias, 2016). Project Fun GCAT—Functional Genomic and Computational Assessment of Threats—aims to create technologies for the industry that characterize sequences of all lengths as benign or harmful.

DNA can also be synthesized using in-house DNA printers. These printers normally can print sequences that are up to 200bp long with decent efficiency. More expensive printers, costing over \$40,000, can produce sequences that are almost 2000bp long (Fikes, 2015). The researcher would then have to stitch the pieces together and amplify the strand to be able to integrate it into an organism. To create an artificially synthesized 1500bp strand, a researcher may take nearly two weeks and spend over \$300, not including the cost of the printer itself (Scott, 2018). Due to the burdens of cost and time, researchers and DIYers prefer commercial DNA synthesis. However, an individual or nefarious actor may turn to a personal DNA printer to avoid screening or detection. To reduce this possibility, some academics have suggested gene printers should be licensed or registered to individuals. A report published by the Venter Institute analyzed licensing and registration for DNA printers and found such a process may indeed help deter a nefarious actor but could be costly to implement. The report also concluded such intervention may be increasingly needed in the future as printer technology advances (Garfinkel et al., 2007). In 2017, Boles et al. reported they had developed a digital-to-biological converter for automated production of biologics, like DNA templates, proteins, and viral particles (Boles et al., 2017). The group hopes to reduce the footprint of their design and bring it to market, probably at a price similar to the BioXP 3200—priced at just under \$50,000 when it hit the market (Fikes, 2015).

With such strides taken in DNA printer technology, ensuring printers do not fall into the hands of bad actors is paramount. Tracking and regulating the printer itself could prove difficult. One proposal is to regulate DNA printer technology by regulating the raw materials these printers use. Traditional DNA printers have used nucleoside phosphoramidites as the raw material to create DNA. Regulating this raw material was determined not very feasible by Garfinkel et al. as it is used by the pharmaceutical industry in large quantities. The study suggested waivers could be issued to pharmaceutical developers to help them more easily obtain nucleoside phosphoramidites if it were to become a regulated substance (Garfinkel et al., 2007).

Future DNA printer technology that expedite long-sequence synthesis like never before may not use raw materials that are commonly used in other industries (Palluk et al., 2018). Regulating such raw materials could prevent a nefarious actor from seeking to synthesize a pathogen quickly without burdening other industries.

#### 3.1.4 Gene Editing Technology

Gene editing technology has been around for a long while, but the current debates surround CRISPR proteins, specifically CRISPR-CAS9. CRISPR is now widely used in synthetic biology research for genome editing in both DIY and institutional settings.<sup>12</sup> There is a split on who should have access to CRISPR genetic editing technology and what types of research it should be used for. With companies like Odin selling directly to consumers, many, including Professor Henry Greely of Stanford University, believe a “balanced regulatory approach” to CRISPR is needed that allows “responsible do-it-yourself [biology] while protecting health and the environment” (Skerret, 2016). Professor Greely and others are also very concerned with regulation of CRISPR human germline editing projects across all laboratories and institutions, as evidenced by the 2015 Napa Policy Forum (Baltimore et al., 2015). The FDA was mandated by Congress in 2016 to not use any appropriated funds for the reviewal or research of a product where a human embryo is genetically edited to include a heritable genetic modification, also known as germline editing (Consolidated Appropriations Act, 2018).

The ethics of human germline editing is an exceptionally important discussion to have and will decide what the future of medical research will look like. With relation to the DIYbio movement, the concern for editing embryos and germline cells is quite low. DIYbio community laboratories are only BSL-1 compliant, with the exception of Counter Culture Labs which is developing a BSL-2 compliant room (Counter Culture Labs, n.d.). To edit human cells, laboratories must be—at a minimum—BSL2 compliant, according to the CDC.<sup>13</sup> To prevent editing of human germline cells using CRISPR, one may look to the Federal Select Agent Program’s Division of Select Agents and Toxins (DSAT). DSAT conducts laboratory inspections to ensure facilities attempting to obtain select agents and toxins are compliant with lab safety guidelines (Buyon, n.d.). Human germline cells are not on the Federal Select Agent List.

As evidenced by the NAS report on Biodefense in the Age of Synthetic Biology and proposals for Fun GCAT, there is also great concern that pathogens could be made more dangerous by precise and knowledgeable gene editing of their DNA sequence. Such concern is another contributor to the calls for CRISPR regulation. CRISPR is currently not regulated, as the US only regulates products of biotechnology and not the tools of biotechnology or synthetic biology.

## 3.2 Biosafety

Biosafety encompasses the practices to ensure worker safety when working with biological systems and to prevent exposure of harmful biological agents in the laboratory or to the

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<sup>12</sup> For applications where precise edits are required in existing organisms, gene editing will remain an important tool. In the future, full genomes of microorganisms with required edits will be chemically synthesized and placed in an organism to achieve a desired function, reducing the need for gene editing tools. Thus, there is an even greater need to improve DNA synthesis screening and DNA printer regulation now.

<sup>13</sup> Biosafety recommendations from the CDC vary depending on the nature of the experiment and the type of human cells used.

environment. Biocontainment, a subcategory of biosecurity and biosafety, is the proper storage of pathogenic biological agents to prevent accidental environmental release. Another major concern with further democratization of synthetic biology is improper biosafety practice in non-traditional laboratory spaces and improper biocontainment of potentially harmful microorganisms. Here, we briefly review concerns of biocontainment as they relate to the DIYbio movement, a major proponent of continued democratization of synthetic biology.

### 3.2.1 Biocontainment

With respect to safety, there is concern the DIYbio community—individuals and labs—could release microorganisms into the environment accidentally or purposefully that could harm people and existing biodiversity. Most DIYbio community labs operate at Biosafety Level 1, using non-pathogenic *E. coli* and yeast. It is possible these microorganisms could be engineered to have pathogenicity or produce harmful toxins by a nefarious actor. IARPA’s Finding Engineering-Linked Indicators (FELIX) program aims to develop technologies capable of detecting engineered organisms to expedite mitigation processes for purposeful or accidental releases of harmful microorganisms into the environment (Dion-schultz, 2017). Individuals that practice DIYbio from their homes may be more likely to dispose of engineered microorganisms improperly than DIYbio community laboratory members.

### 3.2.2 Licensing or Registration for Synthetic Biologists

In an article published by the New York Times, Professor George Church of Harvard University suggested “anyone who does synthetic biology should be under surveillance, and anyone who does it without a license should be suspect” (Baumgaertner, 2018). Church’s concerns have ignited a conversation on whether or not a licensing or registration system for synthetic biologists across academia, industry, and the public should be instituted. Synthetic biology is such a diverse field. There are very few ideas on what a license or registration system would entail, how it would be instituted, and who it would be offered to. Creating such a system that is able to encapsulate and authorize all the practices and techniques in the field is also an exceptionally difficult task.

Obtaining a license in the United States for driving, real estate, and so on requires applicants to pass tests, review materials, and understand responsibilities. A general license for synthetic biology would most likely include trainings on biosafety, bioethics, and best practices. The DIYbio community was founded on safe and ethical practices. A license or registration process would most likely echo these same values. A licensing system may serve as a barrier to deter bad actors but will do very little to deter a motivated, experienced bad actor. A licensing or registration system equipped with trainings could help reduce bioerror, accidents, and promote safe practices. To make licenses or registration effective for deterring bad actors, industry leaders would most likely have to get involved. Commercial DNA synthesis companies or DNA printer retailers could be mandated to sell only to consumers that can present a license or proof of registration. Databases and repositories could also require users to prove they have a license before viewing or submitting sequence data. The Venter Institute suggested a licensing or registration system would be costly to institute (Garfinkel et al., 2007).

The call for licensing raises an important question: *How do we ensure ethical, safe, and informed use of synthetic biology principles, techniques, and findings?* Licenses or registrations may be a way to standardize cultural and technical norms for practitioners, promoting biosafety and transparency. DIYbio is looking for other ways to answer this question. DIYbio laboratories,

like BUGSS and BioCurious, hold workshops and require members to review safety protocols and demonstrate best practices. The DIYbio community is currently working to standardize safety and security amongst its members. In 2017, Open Philanthropy presented two grants totaling \$706,750 to fund a study that will review biosecurity and biosafety practices in the DIYbio community to promote the creation of standards and best practices (Yassif, 2017).

## 4. Recommendations

This section will consider policies that aim to bolster US biosecurity without hampering further democratization of synthetic biology. Section 4.1 considers an additional policy alternative to aid analysis. Recommendations 2-4 do not have a discussion of alternatives. The criteria used are:

*Effectiveness*: Measure of how effective the policy alternative is at promoting democratization of synthetic biology.

*Political Feasibility*: Measure of how feasible the policy will be to enact and execute.

*Safety and Security*: Measure of how the policy alternative will impact the safety of synthetic biology practitioners, the safety of the American public, and overall US biosecurity.

*Cost*: Measure of the economic burden on the US government to enact and enforce the policy and/or the economic toll placed on industry.

## 4.1 Public Use of Synthetic Biology and Licensing or Registration

Policy Alternative 1: Outlaw the practice of synthetic biology by individual members of the public outside of institutional, industrial, or “recognized” facilities.

This policy alternative would make it a prosecutable offense to practice laboratory techniques in synthetic biology (i.e. employ genetic engineering technology for the creation of a new or modified organism) outside of a recognized academic or institutional laboratory. Germany’s Federal Office of Consumer Protection and Food Safety (BVL) is strict on the use of genetic engineering outside of a laboratory that is licensed by the state. BVL has outlawed the use of DIYbio kits as well, threatening a €50,000 fine and the possibility of imprisonment (Federal Office of Consumer Protection and Food Safety, 2017).

Effectiveness: Outlawing the practice of synthetic biology by the public and DIYers would not promote the democratization of synthetic biology. Citizens who are curious about the field will be deterred from learning more about it due to fears of prosecution under the law if they wished to ever practice. The law would not prevent access to synthetic biology knowledge or technical guidance through open-access platforms and the internet. Citizens would not be able to contribute to the field without the ability to conduct experiments.

Political Feasibility: Enacting such a law would receive backlash from constituents. To make a strong argument for such a law, representatives would likely have to argue the law as a way to ensure US biosecurity. Yet, there are a plethora of options the US can take to ensure its biosecurity and biodefense that have not been discussed, many of which are outlined in the Blue Ribbon Report on US Biodefense (Blue Ribbon Study Panel on Biodefense, 2015). Enforcing such a law would be difficult as well, since DIYbio kits are now widely available and DIYers are not on any registered list. Follow up regulations from government agencies restricting the sale of genetic engineering technology to non-members of institutional laboratories would have to be enforced, which would require a lot of input from law enforcement. Congress would have to appropriate additional funds to law enforcement agencies to aid in tracking down law breakers.

Safety and Security: Such a policy would deter members of the public from practicing synthetic biology in the open. DIYers could be driven underground, away from resources that could help inform good safety and security practices. Poor practices could lead to accidental release of microorganisms to the environment and harm brought to less-seasoned practitioners. The NAS study on biodefense recommended the creation of a network of citizen reporting on matters of biosecurity. The FBI has worked hard to develop connections with the DIY community to promote reporting of suspicious activity without sacrificing innovations and progress made in the citizen science community. Outlawing the practices of synthetic biology amongst the lay public would destroy this developing network of reporting, driving practitioners underground.

Cost: Congress would have to appropriate additional funds for use by law enforcement agencies to enforce this policy. Innovations, startups, and, products that are yielded by public practitioners of synthetic biology (DIYers) would be halted, limiting the growth of the US bioeconomy to the contributions of institutional laboratories and recognized members of industry.

**Recommendation 1.1: Continue with no regulations on members of the public that practice synthetic biology outside of an academic or institutional laboratory setting.**

The recommendation is to not institute any direct laws to regulate the practice of synthetic biology at this time.

*Effectiveness:* With no restriction on who can practice efforts of synthetic biology, the field can be freely democratized.

*Political Feasibility:* Maintaining the status quo on regulating public practitioners requires no intervention by government legislative or regulatory bodies.

*Safety and Security:* Maintaining the current system in regard to public practice does not provide a registry to law enforcement agencies which could prove useful in tracking down persons responsible for the accidental or purposeful release of a harmful organism. The current method to promote a network of citizen reporting in the DIYbio community could also prove just as effective for tracking down suspects and also provides law enforcement with information that can help in anticipating wrongful use of a technology or process. In essence, a registry would help reactionary efforts to a biosecurity issue. Building on the current method of citizen reporting provides both anticipatory and reactionary avenues to improve US biosecurity and biodefense.

*Cost:* Maintaining the current system of public practice of synthetic biology will not introduce any new costs to the federal government. The federal government may invest to promote biosecurity by other means outlined in the following recommendations.

**Recommendation 1.2: The Department of Homeland Security, Department of Defense, or National Institutes of Health should employ the National Academies of Sciences to prepare a detailed report on implementing a licensing and registration system for practitioners of synthetic biology.**

A licensing or registration system that promotes best practices, ethics, and safety in synthetic biology across academia, industry, and the general public could prove useful. Commercial DNA synthesis companies and private DNA printer retailers could require customers to show proof of licensure or registration, creating another barrier for nefarious actors. The National Academies should prepare a study to recommend a licensing or registration system that is cost-effective and not burdensome on research and development.

*Effectiveness:* The recommendation does not have an immediate impact on the democratization of synthetic biology. Licensing systems proposed by the National Academies could prove beneficial or detrimental to the democratization of synthetic biology.

*Political Feasibility:* Congress would need to appropriate funds to one of the listed government agencies to allow for the study. Congress could directly appropriate the funds as well but providing a point of contact for NAS in a relevant government agency may prove beneficial.

*Safety and Security:* The study would not provide any immediate improvement to safety or security. A licensing or registration system that is used by industry to determine the legitimacy of synthetic biology consumers could prevent next generation DNA printers from getting into the wrong hands. A licensing or registration system could also be used by practitioners to gain access to online databases and to file commercial DNA orders. A licensing or registration system could be instrumental in deterring nefarious actors.

*Cost:* Congress should appropriate approximately one million dollars to fund this study.

**Recommendation 1.3: The American Institute of Chemical Engineers should prepare trainings for the lay public on biosafety, bioethics, and best practices in synthetic biology and genetic editing.**

A license or registration system would not deter a very motivated nefarious actor. Such a system would best promote safety and ethical practice of synthetic biology using trainings or readings. This could help reduce bioerror, accidental releases of engineered biological cells to the environment. While a license system is years away, immediate action should be taken to promote such a culture of accountability and responsibility amongst individual practitioners. AIChE should work with Daniel Grushkin and Todd Kuiken, recipients of the Open Philanthropy grant on DIYbio biosafety and biosecurity, to develop these trainings.

*Effectiveness:* Trainings prepared by AIChE could help promote best practices amongst DIYers. Trainings could also promote further democratization of synthetic biology in an ethical and safe manner.

*Political Feasibility:* No legislative action or mandates would be required. The study would be conducted at the discretion of AIChE

*Safety and Security:* Trainings for the lay public could help reduce bioerror and promote ethical and safe practices. DIYbio laboratories and the movement itself could make great use of these trainings. Trainings will do little to prevent motivated nefarious actors.

*Cost:* AIChE should pay for the development of these trainings. The trainings could potentially be used for job retraining for chemical engineers looking to work in biotechnology.

#### 4.2 Databases, Repositories, and Open-Access Information

**Recommendation 2.1: Continue with no regulation of databases, repositories, and other sources of open-access information for the time being. The FBI WMD Directorate and the Department of Homeland Security should continue to foster relationships with developers of repositories and databases to develop best practices that do not restrict access to information and promote responsible use of these platforms.**

Many repositories—JBEI-ICE, Registry of Standard Biological Parts, etc.—have taken great strides to screen parts submitted and promote accountability by requesting users to answer a few personal questions. The FBI and DHS should continue to be a forum and a point of contact for up-and-coming information-exchange platforms that significantly reduce the knowledge barriers required in synthetic biology research and experimentation. These open-access platforms, in combination with screening technologies developed by IARPA, could prove useful in creating dynamic screening lists for the industry. Trying to restrict access to pathogenic sequences also hampers a researcher’s ability to analyze these sequences for the creation of potential cures. Actual DURC wet-lab experimentation should not be conducted outside of secure facilities but computer-aided analysis of sequence data could be exceptionally useful for the creation of such curative measures.

*Effectiveness:* The approach will limit the intervention of law enforcement in monitoring databases and registries. These platforms will continue to serve as sources of information and technical know-how for members of academia, industry, and DIYbio.

*Political Feasibility:* This action is a suggestion for the WMD directorate of the FBI and DHS and will not require a set of appropriations or enactment into law.

*Safety and Security:* By expanding its network to leaders of repositories, the FBI and DHS will be able to provide guidance and promote best practices with new platforms aimed at the democratization of synthetic biology knowledge and design. Yet, due to the vastness of the

internet, any motivated actor will still be able to post pathogenic sequence data or information on how to create a harmful product using methods of synthetic biology.

*Cost:* As the FBI and the DHS will not have any direct interventions with the creation or operations of these platforms, there should be no funding required.

#### 4.3 Commercial and Private DNA Synthesis and Screening Technologies

**Recommendation 3.1: The federal government should continue to fund research programs to develop next generation screening technologies for use by the industry as well as law enforcement.**

IARPA should continue to work on Fun GCAT and FELIX. Congress should continue to appropriate relatively similar funds for IARPA research to ensure the life of these projects. Fun GCAT is aimed at providing screening technologies that will be able to predict pathogenicity of DNA sequences that are not well documented or recorded. The technology is aimed to reduce screening costs for industry as well.

Mandating all commercial DNA synthesis companies to screen orders will be costly and could negatively impact the industry, especially smaller firms (Garfinkel et al., 2007). Government intervention in the creation of these technologies is highly favorable for industry stakeholders.

*Effectiveness:* This line of action has no direct intervention with the democratization of synthetic biology. It will instead enhance US biosecurity to prevent potential acts of bioterrorism without directly regulating synthetic biology practices. Practitioners may lose access to harmful DNA sequences if the technology is instituted, which limits the extent of research projects researchers can conduct.

*Political Feasibility:* Congressional appropriations committees need to continue to provide consistent funds to IARPA to see out this project. No further legislative action is required.

*Safety and Security:* Next generation screening technologies will aid in the detection of potentially pathogenic and harmful sequences that are not provided by any “static” controlled substance lists.

*Cost:* No additional funds need to be appropriated by congress. Continuing this line of action will ultimately reduce the costs of sequence screening for commercial DNA suppliers. Cheaper screening technologies are more likely to be adopted and used by a greater number of commercial suppliers. Mandating screening by all gene synthesis companies with current technologies would be unfavorable for smaller firms. Use of new screening technologies that reduce screening costs as a whole may be easier to mandate in the future.

**Recommendation 3.2: The State Department should work in conjunction with IARPA Fun GCAT to begin conversations at meetings of the Biological Weapons Convention (BWC) on defining an international authority to implement such technology and monitor updates to select agent lists and databases.**

IGSC members screen using “static” select agent lists from around the world. Maintaining and updating an international list of pathogenic sequences for use by commercial DNA synthesizers globally would be useful. Representatives of the State Department should consider discussing with world authorities in BWC and industry leaders of the IGSC how technologies from Fun GCAT should be implemented to create a more dynamic screening list for commercial DNA suppliers. Having these conversations now will expedite the institution of these technologies and screening processes at the conclusion of Fun GCAT.

*Effectiveness:* A dynamic international screening list will limit, although minimally, the sequences customers can purchase from commercial suppliers. Legitimate researchers with appropriate credentials may have to conduct follow-ups with the supplier to prove their legitimacy and obtain flagged sequences.

*Political Feasibility:* The United States would not be the owner or be in charge of updating an international screening list. Delegates from the Department of State will first have to determine what actions are requested by state parties of the Biological Weapons Convention before any US legislation could be proposed.

*Safety and Security:* Holding these conversations now will lead to easier adoption of new screening technologies. State Parties of the BWC agreed to meet annually from now until 2020 (UNOG, 2018).

*Cost:* The United States sends delegates to the conventions already. No additional costs will be incurred.

**Recommendation 3.3: Congress should appropriate \$500,000 to the CDC to conduct annual horizon scan studies of DNA printer technology and provide recommendations to the USDA, State Department, and HHS on regulating the raw materials used in these processes.**

Brief and inexpensive horizon scans conducted by the CDC could help determine if novel DNA synthesis printers and the raw materials they use can expedite the creation of a pathogenic sequence with minimal additional workup. The CDC should notify the USDA, State Department, and HHS of its findings and recommendations to add novel raw materials to the Federal Select Agent List. If a recommendation requires a material to be added to the Select Agent List, the CDC should accordingly request an increase in appropriated funds from Congress.

*Effectiveness:* Horizon scans will not impact how synthetic biology is practiced currently by citizens. The findings of these scans may limit the agents that are available to the public down the road, but there will be avenues for citizens to obtain these materials as long as they follow the rules set forth by the CDC.

*Political Feasibility:* Congress should mandate these reviews by including them in yearly appropriation bills. Actual horizon scans would be conducted by the CDC.

*Security and Safety:* Horizon scans could inform entry points for regulating raw materials that are used in advanced DNA printers. Recommending and actually adding substances to the Federal Select Agent List could prevent nefarious actors from printing pathogenic sequences using private DNA printers.

*Cost:* Conducting annual horizon scans will require some monetary input from the CDC. Since the scope of the horizon scan is quite narrow, yearly reports should be completed quite quickly and at low cost. Congress should annually appropriate \$500,000 to the CDC to conduct these analyses.

#### 4.4 CRISPR Gene Editing Technology

**Recommendation 4.1: In the Department of Labor, Health and Human Services, and Education, and Related Agencies Act for Fiscal Year 2020, Congress should appropriate \$1 million to the CDC to work with the Animal and Plant Health Inspection Service (APHIS), Department of Defense, Department of Commerce, and NIH to review new pathogens and cell-types that could easily be weaponized or used for unethical purposes by genetic editing technology. The review should provide recommendations for updates to be made to the**

**Federal Select Agents List. The review should also provide estimates on the costs to regulate and control the recommended additions to the list.**

To keep citizens from conducting germline cell editing or editing of microorganisms that could prove easily weaponizable, the CDC, with the expertise of the USDA-APHIS, DOD, Department of Commerce, and NIH, should conduct an extensive update to the Federal Select Agent and Toxins List. The Division of Select Agents and Toxins conducts thorough inspections of facilities belonging to requestors of certain items on the Federal Select Agent and Toxins List. Adding items to the list will expand DSAT's oversight, triggering additional safety inspections of public, academic, and industrial laboratories. DSAT inspections will ensure laboratories are following proper CDC BSL safety and containment practices.

*Effectiveness:* Public, institutional, and industrial laboratories may need to meet additional requirements to obtain certain microorganisms and agents. Requests may be denied to some of these laboratories. In this manner, the tools of biotechnology, namely CRISPR/CAS9, will still be available to practitioners. Yet, the likelihood of an organism that poses a higher security threat or ethical concern if genetically edited is reduced.

*Political Feasibility:* Through an appropriations bill, Congress should require leadership in the mentioned agencies to complete the review.

*Safety and Security:* These updates will further limit access to a broader set of pathogenic and potentially dangerous microorganisms and agents. Depending on the items added to the list, community laboratories may also receive additional guidance, which could be beneficial in reducing bioerror.

*Cost:* If too many items are added to the list, DSAT and other groups within the CDC may be overwhelmed with verifying all requests. Meeting the demand may require increases in spending. Adding pathogens and agents to the Select Agent List will trigger new export controls that could significantly increase costs incurred by relevant agencies. The review conducted should therefore also provide estimates for costs incurred in adding pathogens or agents to the Federal Select Agent List. Government agencies will most likely require expansions in appropriated funds from congress to expand their regulatory oversight of items on the Federal Select Agent List.

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